Institutional Peer Pressure:

Why pharmaceutical and biotechnology organizations participate in the Orphan Drug Act (1983)

by

Erica Jankelovitz

Mentor: Jason Owen-Smith, Associate Professor of Organizational Studies and Sociology

Department: Organizational Studies

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"How wonderful it is that nobody need wait a single moment before starting to improve the world."

-- Anne Frank

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ABSTRACT

The Orphan Drug Act (ODA) (1983) has stimulated vital research and development efforts within the pharmaceutical and biotechnology industry to develop treatments as well as drugs and products for people affected by rare diseases. The ODA provides marketing and regulatory incentives to firms whose product(s) receive an orphan designation from the Food and Drug Administration (FDA). Due to their small patent population and the organization's likelihood of recouping their costs of investment, the ODA has provided a source of new hope for those patients whose condition would otherwise be likely ignored by pharmaceutical companies.

This study looks at why some organizations elect to participate in the ODA, while others choose to not develop orphan drugs. I apply organizational theories about institutional legitimacy to develop my theory linking a firm's involvement with the public sector to an increasing likelihood of ODA participation. First-time orphan drug sponsors in 2008 were analyzed, and logistic regression was used to estimate the effects of the independent variables related to public sector engagement on the likelihood of a firm developing an orphan drug. Results suggest some support for an organizational legitimacy argument.

INTRODUCTION

Inequalities of health and health care represent a great source of social injustice. It is especially imperative to promote the welfare of those who cannot individually help themselves—those individuals whose medical needs are not being met—because they

suffer from rare diseases and conditions. Presently, the National Institutes of Health (NIH) estimates that there are approximately 6,000 rare diseases affecting more than 25 million Americans ("Fact Sheet", NIH) and the FDA estimates that 85-90% of rare diseases are life threatening, yet effective treatments do not exist for many of these conditions.

Pharmaceutical and biotechnology companies must undergo a costly and time-consuming research and development (R&D) process when developing a new drug. Recent estimates put the costs of development of a new drug at 12 years and $800 million ("Research and Development in the Pharmaceutical Industry", Congressional Budget Office). Because rare diseases affect relatively few people,[1] it is considerably more risky for the pharmaceutical and biotechnology industry to invest in developing a novel drug or treatment. This risk originates from two sources: first, relatively small markets mean that companies are likely to incur financial losses because of the cost of developing the drug or treatment ("Orphan Drug Act", Food and Drug Administration); second, development itself might stall as it will be difficult to meet FDA requirements for testing safety and effectiveness in clinical trials due to the small patient populations ("Developing Orphan Products: FDA and Rare Disease Day", FDA).

Thus, an organizational question arises: how can pharmaceutical and biotechnology companies be persuaded to invest the necessary amount of time, money, and resources into developing the less profitable, but none-the-less vital drugs or treatments for people diagnosed with rare diseases?

[1] By definition affecting fewer than 200,000 people in the United States (National Organization for Rare Disorders Website)

My research focuses on the ODA, a beneficial legislation that increases research and development on drugs and treatments for rare diseases and conditions in the United States. The ODA accomplishes this feat by compensating for the key difficulties associated with orphan drug development. The Act offers financial and regulatory incentives for orphan designated products. These incentives include: "(1) tax credits for clinical trial work, (2) clinical trial planning assistance, and (3) seven years of market exclusivity for the drug in the orphan indication" (Hogan, 1995). Since these incentives are only available to designated orphan drugs, the ODA makes it more likely that a biotech or pharmaceutical company will target rare diseases. Thus, the ODA is structured to provide marketing and regulatory incentives to foster interest and stimulate innovation in markets that have been ignored by the pharmaceutical and biotechnology industry.

Many studies of the ODA have focused on the effects of these market incentives. These more economically inclined papers suggest that market forces alone determine organizations' decisions about drug development. For instance, recent research established that due to the unpredictable R&D pay-off in the orphan disease market, the tax incentives associated with the ODA help to establish a certain revenue potential and thus encourage rare disease innovation (Yin, 2007). Furthermore, another report (Haffner, 1999) notes, "[m]arketing exclusivity for the sponsor has been by far the most motivating incentive [of the ODA])" (p.566) as this effectively protects the company from competition and competing patent claims from other firms.

While I believe market incentives are a critical rationale behind a firm's decision to develop an orphan drug, I think that there is more to the story. I propose that an additional, institutional dimension to the argument must be considered. Specifically, the

institutional legitimacy theory can provide another explanation for why a firm would seek to develop an orphan drug. I employ sociological and institutional theories to explain why some firms choose to develop orphan drugs. In addition to acting in response to economic forces, organizations seek to appear legitimate by following the normative expectations of their societies. As Edelman and Suchman (1997) note, organizations are "cultural rule-followers and see the law as a system of moral principles" (p.479) that they seek to emulate.

My study will provide an important example of "the (…) ways in which law and organizations are dynamically intertwined" (Edelman & Suchman, 1997: 479) by showing law as a principal element in the organizational environment. I will integrate this view with the theory of institutional legitimacy, which expects organizations to adhere to non-compulsory laws (in this case, the ODA) because laws offer indications of broader societal norms.

I hypothesize that organizations that are more closely affiliated with universities, hospitals, and other public research organizations (PROs) are more likely to develop drugs for small patient populations. Institutional legitimacy would predict that publicly affiliated pharmaceutical and biotechnology firms will seek to follow the norms associated with these PROs, such as focusing on the public good to maintain a positive public image (Owen-Smith & Powell, 2005). I therefore argue that orphan drug development is a vital way for an organization to gain legitimacy with its constituencies. Pursuing normative goals can also lead organizations to participate in the ODA.

My research takes an in-depth look at organizations that were first-time sponsors of an orphan drug designation in 2008 in order to discern what factors lead some

organizations to participate in the ODA while others choose not to participate. When approved for an orphan drug designation, the product is considered to have "orphan status"; an orphan designation is required in order to quality the filing organization for the various incentives offered in the ODA ("Designating an Orphan Product: Drugs and Biologics", FDA). Building on previous research that concentrates on the organizational effect resulting from the more obvious economic incentives established in the ODA, the organizational theory of institutional legitimacy can offer a unique perspective regarding how the ODA has promoted the development of drugs and treatments for rare diseases.

THEORY & HYPOTHESES

This study presents an opportunity to analyze how organizations react to laws. In our Democratic society, laws can be perceived as an expression of societal norms and values (Dowling & Pfeffer, 1975). Michael J. Sandel (2009), Professor of Government at Harvard University, also remarks on the interpretation that laws "reflect a moral judgment" (p.53) and further remarks on the "coercive force of law to promote notions of virtue or to express the moral convictions of the majority" (p.60). Thus, I contend that the ODA reflects particular norms that are important to the public majority and establishes an effective way for firms in the pharmaceutical and biotechnology industry to gain legitimacy with their constituents. Participating organizations are thereby actively pursuing an orphan drug as an organizational effort to become legitimate within their larger social environment. As suggested in institutional theory, adhering to social expectations will play in important role in organizational survival, as well as have a positive impact on organizational success (DiMaggio & Powell, 1983).

It is somewhat of a truism that an organization's environment influences its decisions. However, institutionalists argue that conformity to social expectations will contribute to organizational survival, while increasing the likelihood of organizational success (DiMaggio & Powell, 1983). The institutionalist view suggests that drug development choices will in part be determined based on the signals about the morality a decision represents to key constituencies.

I contend that organizations seek public approval as a means of increasing their chance of survival. A firm that has gained legitimacy with their constituents has succeeded in gaining public approval. Thus, "[f]irms make normatively rational choices that are shaped by the social context of the firm" (Oliver, 1997: 700) in order to achieve this level of legitimacy. There are a multitude of forces that shape a firm's social context in which their decisions are embedded, including government, partner organizations, and societal expectations (in particular, norms and values).

I maintain that a company participating in the ODA attempts to follow and openly demonstrate societal norms (such as principles of justice, fairness, having a concern for the public good, etc.) through their organizational activities and decisions. A fundamental method an organization can employ to become legitimate is to "adapt its output (…) [and] goals (…) to conform to prevailing definitions of legitimacy" (Dowling & Pfeffer, 1975: 127). Hence, by filing an orphan drug designation, the company is attempting to increase their legitimacy, thereby ensuring their survival (Meyer & Rowan, 1977). Therefore, the law influences and shapes our society and the corporate world by changing the calculations organizations use to make choices. The organization's decision to develop an orphan drug is strongly linked to the regulating importance of different

audiences; while a firm that is in the public sphere will favor basing the decision on normative pressures from partners, funders, and patient groups, a firm that focuses on economic incentives will make a decision that seems to be in the best interest of their shareholders. I believe the ODA succeeds in aligning these two sets of interests.

In terms of practices adopted in order to increase legitimacy, DiMaggio and Powell (1983) simply suggest that "the very fact that [these strategies] are normatively sanctioned increases the likelihood of their adoption" (p.148). This particular rationalization helps to explain the dramatic increase of orphan drug designations and participation from firms since the enactment of the ODA in 1983 (see Figure 1). Before the ratification of the ODA, only a handful of orphan drugs and treatments existed; as of February 2009, more than 1,700 medicines have been designated as orphan drugs ("Developing Orphan Products: FDA and Rare Disease Day", FDA).

[Figure 1 Here]

Institutional theory would thus suggest that some types of pharmaceutical and biotechnology firms are more likely to take advantage of the ODA, regardless of economic incentives. As hypothesized by Dowling and Pfeffer (1975), "[w]hile legitimacy is a constraint on all organizations, it is likely that it affects some organizations more than others (…) because (1) some organizations are considerably more visible, and (2) some organizations depend relatively more heavily on social and political support" (p.133). As I postulate, being more closely tied to the public sector will increase the chances for an organization to seek an orphan drug designation as a legitimating activity. A firm conducting business in the public sphere faces a greater normative pressure from its partners, funders, and its audience of consumers. As laws

reflect norms, an organization making decisions based on appeasing audiences in its public sphere, and whose legitimacy depends on approval from their constituencies, will be more inclined to develop an orphan drug through the incentives offered in the ODA. This hypothesis is echoed by Dowling and Pfeffer's argument that "because regulated organizations are more heavily dependent on acceptance by the environment for their economic well-being, they engage more in activities to link the organization with its environment" (p.133).

I aim to demonstrate in my research that the law shapes organizational behavior for normative as well as economic reasons (Edelman & Suchman, 1997). Contrary to a view that strictly takes into account an organization's economic motivation, this analysis argues that "material costs and benefits are, at best, a secondary concern. This perspective sees organizations as cultural rule-followers and sees the law as a system of moral principles, scripted roles, and sacred symbols. Thus, organizations look to the law for normative and cognitive guidance, as they seek their place in socially constructed cultural reality" (Edelman & Suchman, 1997: 482). In short, law becomes ingrained into an institution's environment and subsequently establishes a vital way in which an organization can gain legitimacy with their constituencies.

Institutional theory addresses the pursuit of organizational legitimacy as the ultimate factor underlying organizational decisions. Furthermore, an organization's participation in the ODA is consistent with Meyer & Rowan's (1977) theory of how "organizations are driven to incorporate the practices and procedures defined by prevailing rationalized concepts of organizational work and institutionalized in society. Organizations that do so increase their legitimacy and their survival prospects" (p.340).

My study is consistent with this theory as it establishes developing an orphan drug as a valuable approach to the process of legitimization for organizations in the pharmaceutical and biotechnology industry, and presents legitimacy as the principal factor leading organizations to seek an orphan drug designation. These "prevailing rationalized concepts" stem from the institutional environment. In this case, I argue that organizations with institutional environments enmeshed in the public sector follow established publicly valued norms and sentiments in order to increase the organization's legitimacy and increase the organization's chance of survival.

The primary norm my study will focus on is participating in business activities that foster public good in order to maintain a positive public image (Owen-Smith & Powell, 2005). In this case, that public good is directly represented through the ODA, and quantifiably, through the filing of an orphan designation.

I hypothesize that public sector engagement increases the likelihood of filing an orphan drug designation. This affiliation between an organization and the public sector creates an important dimension in terms of pressure to conform to public expectations of societal norms and values when compared to firms that are less involved in the public sphere. As institutional theory predicts, an organization is seeking to gain legitimacy and legitimacy is seen through the eyes of key stakeholders in their environment. Therefore, closer affiliation to the public sector defines an organization's key stakeholders. As an organization's actions are evaluated in terms of the context of the larger social system, greater public sector engagement augments the necessity for the firm to engage in behavior that is congruent with the social values and norms in order for legitimacy to be conferred.

I predict that firms that are more closely tied to the public sector are more likely to file an orphan drug designation. I define public sector involvement through measures from three sources of data: number of NIH grants, number of ties to PROs as found in filings through the US Securities and Exchange Commission (SEC), and number of publications as found through the Pubmed database—an online, digital archive of biomedical and life sciences journal literature. Higher values for each of these measures suggest an organization is "closer" to the public sector. For those organizations, public good concerns may loom large because a larger proportion of their environment is composed of partners and sources of funding who also emphasize public goods.

I propose three hypotheses dealing with public sector engagement and affiliation:

Hypothesis 1: NIH grants

NIH grants will increase the likelihood that an organization will file for an orphan drug designation. NIH grants are taxpayer funded, increasing the public's stake in the organization's activities. Furthermore, since it can be argued that receiving a grant can increase the public's interest and awareness of organizational decisions, these organizations can be considered more visible, and increase the firm's efforts to seek legitimacy (Dowling & Pfeffer, 1975).

Hypothesis 2: Partner Public Research Organizations (PROs)

Ties to PROs translate to a greater probability that the focal organization will seek to develop an orphan designated product. PROs are highly visible institutions in the public environment; therefore, a firm's affiliation to such an institution increases the firm's visibility to key stakeholders. As mentioned in an earlier argument by Dowling

and Pfeffer (1975), visibility impacts the need to perform legitimizing activities. Formal ties to PROS provide a defining characteristic of the organizational environment of the firm and thus increase the chances for the filing of an orphan designation. Aside from the more obvious benefits of access to research and other resources, affiliations to PROS are effective tools for achieving legitimacy since PROs "have a strong base of social legitimacy" (Dowling & Pfeffer, 1975: 127). These formal ties are observed as "the existence of transactions tying organizations to one another: such transactions (…) include formal contractual relationships" (DiMaggio & Powell, 1983: 148) such as licensing ties, but also includes other collaborative relationships, such as research and development (R&D) ties.

Hypothesis 3: Publications

Two or more publications are predicted to increase the likelihood of an organization filing for an orphan drug. Publications based on research conducted by pharmaceutical and biotechnology companies provide a third dimension to an organization's relationship to the public sector. The fields of academic research, associated with PROs, and commercial R&D, associated with for-profit firms, are institutionally distinct. According to Dasgupta and David, (1994), "[w]hat matters is the socio-economic rule structures under which the research takes place, and, most importantly, what the researchers do with their findings" (p.495). While commercial institutions seek to benefit by patenting their findings, PROs can be expected to value publications as a means of sharing their research with the public domain.

However, these motivations are not mutually exclusive. It can be to the advantage of profit-seeking firms to participate in open, collaborative activities such as publishing.

The willingness to publish information is associated with traditional public sector norms of open science and information disclosure (Owen-Smith & Powell, 2005). The collaborative and public nature of publishing "encourages its use by others, and in so doing, increases the reputation of the researcher" (Powell & Owen-Smith, 1998: 254); as the author is associated with a particular firm, this reputation carries over to the institutional level and increases the legitimacy of the focal organization. The resulting legitimacy conferred upon the firm is of a particular nature, as these organizations are supposed to be oriented toward property (i.e. patents) and profit and instead of seeking these financial rewards for the firm, publishing serves as a symbolic dedication to the public sector and to the academic norm of serving the greater public good.

In short, it is in the organization's best interest—both in terms of reputation and in terms of attracting research partners—to publish. Companies who publish are trying to benefit from engagement in the public domain of science and creating opportunities with the PROs that control that sphere. This behavior also speaks to the reason behind a firm's mirroring of social norms that are commonly just associated with PROs and other organizations within the academic research field.

DATA AND METHODS

Data collection methods and rationale: Participating ODA organizations

In order to test my hypotheses, I first had to identify all organizations that have participated in the ODA since its enactment in 1983. I was able to retrieve a list of all orphan drug designations and their respective sponsors through the FDA website[2]. I ran

[2] http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm

this search after limiting the results to those found between the period of January 1st, 1983 to September 10th, 2009 (the day I performed the search). I retrieved 2,067 entries as a result of my search.

I then assigned a unique identification number to each entry based on the organization that filed the orphan request. I determined organizational identity by checking organizational ownership at the time that the orphan drug designation was received. Ownership information was primarily determined using the Onesource database[3]. Where an organization was not listed in the database, I would determine the ownership from information (such as press releases) found on the company's website or via lexis or SEC searches. When a company lacked a corporate website, I would attempt to find the company using a variety of other credible business information sites. These sites were: Manta[4], Linkedin[5], and Bloomberg[6]. If it was unclear exactly when the organization assumed a new identity (in the case of a merger or an acquisition), I would use various online news sites[7] to retrieve an archived article that provided new insights.

Each organization received a different filer identification number except in cases where the organization was a wholly-owned subsidiary of a parent company. In this case, I would assign the same filer identification number as that parent company (if the parent company was included in the data set) or another filer identification number to reflect the change in organizational identity. There were multiple cases where an organization was assigned different filer identification numbers for this reason; this event occurred when

[3] http://globalbb.onesource.com.proxy.lib.umich.edu/homepage.aspx
[4] http://www.manta.com/
[5] http://www.linkedin.com/
[6] http://www.bloomberg.com/?b=0&Intro=intro3
[7] nytimes.com, http://www.washingtonpost.com/, cnn.com

an organization received an orphan designation and then was later sold to another company (who assumed ownership) and then after the official sale date received another orphan designation. Another filer identification number would then be created and assigned to the "new" organizational entity. These steps allowed me to create the first data set.

After this stage, I determined for each filer identification number (as multiple organizations could now be associated with the same filer identification number) the location of the firm/main headquarters. As I am interested in organizational reactions to laws created and implemented here in the United States, I then created a second data set that included only those firms located or have headquarters in the United States. I determined the location using the same data collection process as when assigning filer identification numbers—methodically going through the list of sites until I found the information.

From this second data set, I constructed a third data set which limited the data to orphan drug sponsors that received their first orphan designation in 2008. I am interested in the forces that initially lead an organization to participate in the ODA and for this reason, I wanted to focus on the organizations that received their first orphan drug designation in 2008. The rationale behind choosing this particular year will be elaborated on later under the subheading "Why 2008?". All three data sets were constructed using Microsoft 2007 Access software. My final step was to eliminate non-firm from the data set (i.e. research institutions, hospitals, Universities, etc.). After this process was complete, there were 37 organizations that received their first orphan drug designation in

2008; I will hereinafter frequently refer to this particular set of organizations as "orphan drug sponsors".

Data collection methods and rationale: Defining the "risk set"

In order to accomplish the intents of my research, I also had to gather information for a separate set of organizations that could have filed for an orphan drug, but chose not to—this set of organizations served as my "risk set". By comparing this population to a significant sample of organizations from the population of organizations that have participated in the orphan drug act, I drew some conclusions. My "risk set" was determined by compiling a list of all organizations that are in the process of sponsoring, or had in the past sponsored a clinical trial. A list of these organizations was found through an NIH sponsored database website[8] A clinical trial is a mandatory research study conducted by the sponsor organization(s) in order to answer a health-related question; usually, clinical trials are done to test the safety and effectiveness of a drug or device, and these studies are completed using protocols approved by the FDA ("Basic Questions and Answers About Clinical Trials"). Therefore, any pharmaceutical or biotechnology company looking to produce any drug, treatment, or product for use in the United States must have completed, be in the process of completing, or be in the planning stages of performing a clinical trial. For this reason, it can be determined that a company who is listed as being in any stage of a clinical trial, could plausibly have pursued an orphan drug or product but for whatever reason had not done so.

After limiting the studies to phase 1 United States sponsored trials in the time period of September 10th, 2007-September 10th, 2009 (as the database and information for

[8] http://clinicaltrials.gov/ct2/home

clinical trials became active in 2007 and I had executed the search for orphan drug sponsors on September 10th, 2009) 3,309 entries were found matching the search criteria. I restricted the entries to phase 1 trials in order to reduce the number of results, and also because the final "risk set" would be better suited comparatively to the orphan drug sponsors (organizations that received their first orphan designation in 2008). This is because an "orphan designation" signifies that a product could be used to treat a rare disease, but does not indicate that the product has received marketing approval (as is the case of products that have an "orphan approval"). Clinical 1 trials are the first stage of testing in human subjects and therefore, the sponsor has also not been given marketing approval.

I then followed the same steps as described (above) in the first subheading of "Data collection methods and rationale: Participating ODA organizations" in assigning filer identification numbers for the "risk set" of organizations. I constructed the three corresponding data sets using Microsoft Access, and eliminated non-organizations from the data set. The set of prevailing organizations that had a "first" clinical trial in 2008 (although it may very well not be the first clinical trial as the database began in 2007 and thus is not complete) was then randomized and the top 41 organizations were selected to be analyzed as the representative sample of "risk set" organizations. I will hereinafter frequently refer to these organizations as "non-orphan drug sponsors". 41organizations were chosen because that was approximately the same number of orphan-drug sponsors in the data set.

Independent Variables

My study focused on examining organizational factors to ascertain whether seeking institutional legitimacy led a firm to participate in the ODA. I have carefully selected these factors as best representative of public sector affiliation: NIH grants, formal ties to PROs, and publications.

Excluding formal ties to PROs, these measures were all accessible and relatively straightforward to collect. NIH grants were found using a government sponsored database deemed the "project reporter"[9] and publications by the organizational actor (listed along with the organization's name) were found by searching through the Pubmed database[10]. Formal ties to PROs were difficult to find, as I was utilizing the SEC Edgar Database[11]. If the organization was public and had associated 10-K's or an S-1 for the years of 2006-2008 corresponding to the years I collected data for (please refer to subheading "Why 2008?" for further explanation on why those years were selected). I was able to read through the company forms and record the formal tie(s) to a PRO, for example a research and development agreement between the focal organization and the PRO. However, as the majority of these companies do not fit into those specifications, I was unable to collect information on the existence of formal ties for a majority of the organizations as there is no systematic source of information on ties for privately owned firms.

Control Variables

There are a variety of variables which studies may cite as explanations for why a firm seeks an orphan drug designation; among these variables are the location of the firm, the age of the organization (derived from the founding year of the firm), size of the

[9] http://projectreporter.nih.gov/reporter.cfm
[10] http://www.ncbi.nlm.nih.gov/pubmed/
[11] http://www.sec.gov/cgi-bin/srch-edgar

organization (in terms either relating to the number of employees or annual sales), and if the company is publicly/privately traded. These factors serve as my control variables. While I considered each of these explanations to be important factors, I argue that these factors do not entirely account for the organizational decision to seek an orphan drug designation. I collected this data on both sets of organizations mostly from the Onesource database, and also from the same websites utilized when assigning filer identification numbers (see the "Data collection methods and rationale: Participating ODA organizations" subheading).

Why 2008?

There are three main reasons for examining first time orphan drug sponsors in this particular year. Firstly, 2008 occurs two full decades after the last amendment was passed for the ODA. I contend that in this case, the law is fundamentally stable in the sense that it has remained unchanged for a significant period of time. Secondly, the trend of orphan designations filed is relatively stable between the years of 2000-2008 (refer to figure 1) and since I am analyzing organizations in terms of "modern" norms, I wanted to pick a year within this time period. Lastly, and perhaps most importantly, I chose 2008 because it is the only complete year of data found in the clinical trials database, and those organizations serve as my "risk-set" for comparative use to my list of first time orphan drug sponsor organizations in 2008.

Why Two or More Publications?

I contend that one publication is not enough to justify any significant affiliation with the public sector. A threshold of two or more publications, especially when taking

into account the smaller organizations, indicates a firm's commitment to sharing their findings with the public domain, and therefore, indicates public sector engagement. As shown in figure 2, this cut-off is justifiable as two publications are between the average number of publications for the two types of organizations in the data set—orphan drug sponsors and non-orphan drug sponsors (as signified by receiving or not having an orphan drug designation).[12]

[Figure 2 Here]

Analytic Strategy

After this data set was finished and I was able to collect information on my independent and control variables for all 78 organizations. I then imported this excel file into Stata and generated a variety of descriptive statistics (see Table 1). I was then able to complete a logistic regression analysis of the data to test my hypotheses regarding organizational legitimacy. The independent variables act as the determinants of whether a firm will develop an orphan drug. My dependent variable was whether an organization received an orphan drug designation in 2008. The outcome of this test predicts the likelihood of a firm to develop an orphan drug is greater if the firm has a greater affiliation with the public sector.

[Table 1 Here]

I ran five different models. These logits included three indicator variables, which were created corresponding to the three independent variables; these dummy variables designate a value of either 1 or 0 ("1" signifies that something is true, i.e., an organization

[12] Note that all findings are robust to a threshold of 2, 3, and 4 publications

receives a "1" if they have any NIH grants). In the case of publications, the indicator variable contains a value of "1" if the firm has two or more publications. The existence of PRO formal ties could not be included as there were only 23 observations and thus, too few observations to perform a logit.

RESULTS AND FINDINGS

Table 1 reports descriptive statistics for the data in the study. As is indicated in the table, on average, sponsors that received an orphan drug designation in 2008 were younger firms than non-orphan drug sponsors. Also it is extremely important to recognize that, comparatively, orphan drug sponsors were significantly smaller in size in terms of both their number of employees, as well as their annual sales. The average number of employees in 2008 for orphan drug sponsors was 20.22 , while for non-orphan drug sponsors it was 1,723.194 (with standard deviations of 40.406 and 5,105.287, respectively); the average sales in 2008 for orphan drug sponsors was 6.700 (in millions) and the standard deviation was 9.857, and 636.815 (in millions) for non-orphan drug sponsors with a standard deviation of 1,736.502. Both sets of organizations were remarkably similar in terms of mean number of NIH grants between 2006 and 2008. Orphan drug sponsors had a mean of 0.324 and a standard deviation of 1.547, while non-orphan drug sponsors' mean number of NIH grants were 0.463 and a standard deviation of 1.362. Both sets of organizations are also very comparable in regards to the mean number of ties to PROs, although the mean was slightly higher for orphan drug sponsors than for non-orphan drug sponsors. With regards to formal ties to PROs, orphan drug sponsors' had a mean of 1.778 and a standard deviation of 1.856, while non-orphan drug

sponsors had a mean of 0.714 and a standard deviation of 1.437. For the measure of the number of publications during this time-period, orphan drug sponsors had a mean number of 2.811 and a standard deviation of 5.995; non-orphan drug sponsors mean was 1.854 and had a standard deviation of 3.883. Overall, using the measures of NIH grants, ties to PROs, and publications in order to quantify public sector engagement, it appears that orphan drug sponsors are smaller in size, yet approximately equivalently connected to the public sector as non-orphan drug sponsors.

Table 2 reports pairwise correlations among all measures calculated using the available information for each pair of variables. The number of cases in which each correlation is based on is also recorded in the table. This approach ensured that for each pair of variables, I utilized the maximum amount of data available. As expected, as displayed in Table 2, the two measures for organizational size (number of employees and annual sales) were positively correlated with the age of the organization, thus showing that older firms tend to have a greater number of employees and have a larger sales output than firms that are in their earlier stages of organizational life. Both measures for organizational size were also shown to have a negative correlation with number of NIH grants and number of ties to PROs, but have a positive correlation with the remaining predictor variable, which is the number of publications. This finding may be due to the fact that an organization that is more economically viable, thus having a larger sales output and the ability to employ a larger work-force, will not seek to secure outside funding from the NIH. A company searching for funding and/or research partners will frequently team-up with PROs. Therefore, using the same logic of economic vitality, a larger organizational size could signify a reduced need to rely on PROs for R&D

purposes. Following this reasoning, a firm seeking fiscal aid and a secure R&D outlet would therefore tend to be smaller, and less economically stable (in this case, referring to sales) and for this reason publishing would benefit the firm as it engenders a greater opportunity for exposure to prospective PRO partners. It is also worth noting that larger firms may have more research employees, thus allowing some members to focus on producing publishable work. These effects could also be an artifact of missing data for the two measures of organizational size. This point will be elaborated on when addressing the sensitivity analysis I performed.

Pairwise correlation relationships among the independent variables are also found in Table 2. The data reports that NIH grants and ties to PROs have a positive relationship. Owen-Smith and Powell (2004) note that "[t]he NIH is the largest funder of biomedical R&D in the world and the primary recipients of its grants are PROs. R&D grants to commercial biotech firms are a relatively new phenomenon and reflect the research capacities of DBFs [defined as independently held, profit seeking firms involved in human therapeutic and diagnostic applications of biotechnology]" (p.19). The NIH may also grant assistance to research that has a greater chance of succeeding. An argument can therefore be made for how ties to PROs will increase a company's chances of receiving an NIH grant; the reasons for this may stem from the particular types of connections maintained between the organization and the PRO, the best example being an R&D or a license tie to certain technology owned by a PRO. It is very possible that when the NIH awards a grant to a for-profit firm, the NIH is aware that the organization is by some means working with a PRO on the basic research. Furthermore, the chances are higher for a for-profit firm to receive an NIH grant if the firm has ties to a PRO that

has conducted previous "proven" research and if the firm is incorporating this particular information in the R&D for their product. Additionally, publishing entails that the research has undergone peer reviews and therefore the NIH may view the company's research as more legitimate in terms of having a greater likelihood of producing a successful result. This argument also makes sense regarding the slightly positive relationship found between NIH grants and publications.

Furthermore, Table 2 depicts that ties to PROs and publications are negatively related. It seems that for an organization, more ties to academia is associated with less publications. This is, indeed, a confusing finding. This effect could be a function of missing data, especially given the difficulty of collecting information for ties to PROs for private companies. Earlier in this section I argued that publishing opens up opportunities for a firm to establish business ties with PROs, as publishing places the firm's research in the public domain of science and this both makes them more aware and attentive to PROs that dominate that sector, and also vice-versa. A correlation for the 23 observations used in determining the relationship between NIH grants and ties to PROs, as well as between ties to PROs and publications, was then performed[13]. This test revealed a correlation factor of -0.0952 between NIH grants and publications. This correlation makes sense using the earlier argument. As already contended, if a firm has publications then it pays greater attention to PROs. Ties to PROs increase the firm's chances for receiving an NIH grant. When companies pay more attention to PROs it becomes more important for them to establish legitimacy with those institutions, as they view PROs as the dominating form of institutions in their environment. The company is influenced by the broader

[13] This test was performed using listwise deletion of missing data instead of the pairwise deletion of missing case whose results are reported in Table 2.

environment, and this leads the company to develop an orphan drug as a mechanism for gaining legitimacy in the institutional environment in which they operate.

[Table 2 Here]

Table 3 reports logistic regression models that test the impact of public sector engagement on ODA participation. In Model 1 of Table 3, only control variables (age of company and if they are publicly/privately traded) are included[14]. Age is statistically significant, and the negative coefficient suggests that older firms are less likely to seek an orphan drug; this result is seen in Models 2-5 as well. Model 1 also implies that publicly traded firms are not different from private firms. Being traded therefore does not help to explain the difference between organizations that receive an orphan drug designation, and those who do not.

Model 2 includes the control variables and the dummy variable for NIH grants. The results of Model 2 can therefore begin to address Hypothesis 1 on NIH grants by assessing its independent effects. These results reveal an interesting finding: NIH grants have a significant negative effect on the filing for an orphan drug, thus indicating that firms that have one NIH grant are actually *less* likely to seek an orphan drug designation. This finding contradicts my first hypothesis. I consider reasons for this reaction in the "Discussion" section below.

In Model 3 of Table 3, only the effects of the control variables and the dummy variables for publications are measured. We see that when added independently, publications do not have a statistically significant effect on the dependent variable.

[14] Missing data makes the use of organizational size measures untenable in these models. I included them in the sensitivity analyses presented in Table 4 below.

However, a better suited model is presented in Model 4. In addition to the control variables, this model also adds both independent variables—NIH grants and publications—to the logit. Model 4 in Table 3 reveals a statistically significant result supporting Hypothesis 3. This model shows that firms that have two or more publications are more likely to get an orphan drug designation. This model also demonstrates the effects of having an NIH grant. In this particular model, NIH grants once again suggest a statistically significant negative effect on an organization's chances of having an orphan drug designation (again, justification is provided in the "Discussion" section). Reiterating my earlier argument, possessing NIH grants might also make it easier to raise other funds because peer review success might reassure investors about the quality of a company's research.

Model 5 tests the control variables and also introduces a vital facet to the analyses: the interaction of having an NIH grant *and* two or more publications. This interaction is particularly important to the research, as this logit tests the possibility that having both two or more publications *and* an NIH grant would generate an even more likely prospect of developing an orphan drug. However, this interaction does not prove to have any statistical significance, thereby demonstrating the superiority of Model 4. Therefore, the existence of two or more publications and an NIH grant does not make a difference in predicting ODA participation. Hence, Model 4 is the best fitting model. It offers support for one of my hypotheses (Hypothesis 3) and disproves the other (Hypothesis 1).

[Table 3 Here]

The previous analyses present evidence that public sector engagement significantly influences an organization's likelihood of pursuing an orphan drug. In order to determine the robustness of the study, seven additional models were created. These models were all variants of Model 4 from Table 3. The results of the sensitivity analysis are presented in Table 4. The models were created taking into consideration the importance of the influence of organizational size, assessing the effect of missing size data, as well as taking into account the existence of two outliers—one outlier associated with NIH grants and the other outlier corresponding to the publications variable.

The results of Model 1 demonstrates that the addition of the first measure of organizational size, the number of employees in 2008, is not a statistically significant factor and the previous effects of NIH grants remain significant in terms of its negative coefficient, and the predictor variable of two or more publications remain statistically significant, thus lending itself to further support Hypothesis 3 predicting that the existence of publications will increase a firm's chance of seeking an orphan drug. Thus when accounting for size of employees in the model, the effects found are robust. Publications have a positive effect on the likelihood of being involved in the ODA, and this effect remains true no matter how many employees in the firm. However, the results of Models 2-7 demonstrate—in regards to previously drawn assumptions from the models found in Table 3—some sensitivity to the different specifications.

Model 2 helps to determine whether the findings presented in Table 3 are artifacts of taking into account the number of employees for firms that don't have missing employee size data. Results of Model 2 show that the variable denoting two or more publications is no longer statistically significant. In Model 2, however, the effect

disappears suggesting that it depends on the cases where I could not locate information on size. This finding indicates that the cases with missing data for size of employees are responsible for why the relationship changes between publications and ODA participation; one explanation that support lends itself to is that the cases where size data could not be found also were firms that had a large number of publications, so when these cases were lost the effects were modified.

Model 3 in Table 4 suggest that the disappearance of the independent variables' main effects is a function of the size variable (in this case, annual sales). In this case, having an NIH grant and having two or more publications cannot fully explain why some organizations participate in the ODA, while others abstain from taking part in producing orphan drugs. Model 3 demonstrates that after taking a size variable (annual sales) into account, these predictor variables no longer act as accurate measures for calculating the likelihood of a firm pursuing an orphan drug. Sales, as well as the number of employees working for a company, represent how economically well off the company is. The more sales a company has, the greater the company's financial activities and hence, the more likely a company can attract a larger, and more skilled group of personnel. Both these measures are therefore connected to a better economic standing for the company in its environment.

Likewise, in Model 4, when taking into account the size of sales for firms that don't have missing sales data, both independent variables are no longer statistically significant as they were in Model 4 in Table 3. The explanation for this is related to the outliers and will be elaborated on below. Taken together, Model 1 and Model 2 provide insight into how controlling for size might alter my findings.

After performing a sensitivity analysis that allowed for viewing the effects of outliers, it can be determined that the previous finding on publications supporting Hypothesis 3 is sensitive to two outliers. Model 5 excludes the outlier for NIH grants and while NIH grants remain a significant result, publications lose their significance. This outlier has been identified as Armagen Technologies, Inc. and has 9 NIH grants—approximately 6 standard deviations from the overall mean for both sets of organizations (orphan sponsors and non-orphan sponsors)[15]. As demonstrated in the effects of Model 6, when excluding the outlier, the effects of having two or more publications lose their significance, although having an NIH grants still remains significant. This particular outlier organization is BioQuant, Inc.; it has 32 publications, resulting in almost 6 standard deviations above the overall mean number of publications for all organizations[15]. Figure 3 provides a visual display of these outliers. Model 7 corroborates this point, as the effect of having an NIH grant remains statistically significant, although the coefficient is negative thus undermining Hypothesis 1. I posit an explanation for this phenomenon that relates to the firm already having a subsidy and thus not needing to turn to producing an orphan drug as a mechanism for abating the risk associated with R&D.

[Figure 3 Here]

When excluding both outliers (as illustrated in the results of Model 7), the negative coefficient for NIH grants once again suggest that an organization that has an NIH grant will be less likely to be involved in the ODA. Although the factor of the

[15] Please note this analysis was completed separately from the results presented in Table 1, as it does not separate the organizations in the risk-set from organizations that have received their first orphan drug designation in 2008.

existence of an NIH grant is statistically significant, the existence of publications remains insignificant. This point has already been demonstrated, as it was revealed that this finding was sensitive to one outlier. My finding regarding publications is sensitive both to controls for sales volume and to the effect of outliers—my finding regarding NIH grants is more robust, but still sensitive to sales volume.

[Table 4 Here]

DISCUSSION

The dependent variable measure, receiving an orphan drug designation in 2008, was selected due to its clear association with participation in the ODA, as only after a drug has received the designation can it be eligible for the incentives presented in the ODA. The independent variables were carefully chosen to indicate public sector engagement, and also chosen on the relative availability of the information and the ease of collecting the data.

Although my findings do not support Hypothesis 1, I believe I can provide an explanation. An NIH grant essentially provides a firm with a subsidy to help cover the immense costs associated with R&D. As this government-provided resource presents a guaranteed source of fiscal support for the firm, the organization would therefore have no need to seek an orphan drug as a mechanism for combating the inherent risk undertaken in the R&D process as the ODA provides a level of "certainty" for a firm's return on their R&D investments once their drug receives an orphan designation. In other words, the benefits of NIH grants may substitute for some of the benefits offered under the ODA.

This very plausible explanation helps to clarify why a firm that receives an NIH grant is less likely to be involved in the ODA.

This study has demonstrated a relationship between public sector engagement and a greater likelihood of participating in the ODA, specifically linked to support for Hypothesis 3. Thus this study affirmed that a firm that had two or more publications had a greater likelihood of developing an orphan drug. However, as shown in Table 4, the findings show that the two variables depicting firm size predict different outcomes; thus, when calculating an organization's decision to develop an orphan drug, the firm's size of sales is weighted differently than the firm's size of employees. More employees don't make a difference in a firm's decision to seek an orphan drug designation, while more sales diminish the importance of having an NIH grant or having two or more publications.

There are important differences between the two types of size measures that may help to explain my various findings. Both of these variables are valid ways of measuring company size, but individually they are not the most appropriate for all purposes. Company size, in terms of employees, is useful for addressing personnel resource capacities. An organization with a greater number of employees can use the advantage of size to influence their environment by employing and attracting a skilled workforce. The variable of annual sales is related to financial resources; the greater the amount of annual sales, the greater the cash flow and hence, the organization's market share. Both of these measures are useful for attracting other investors, including support from venture capitalist funds. I assume that size is correlated with company growth and the ability for expansion. Therefore, it is reasonable to believe that more sales diminishes the

importance of having an NIH grant or having two or more publications because the firm is economically well off and is therefore it is not a priority to look for a subsidy or other outside funders. This same logic applies to the dependent variable (participating in the ODA) as sales volume is negatively related to orphan drug applications for firms where I have data.

The disappearance of the independent variable relating to publications effect when taking into account the size of sales for firms that don't have missing sales data can be easily explained: both outliers lack employee data, and shown by Model 5, Model 6, and Model 7, excluding just one of the outliers removes the effect. Since both outliers lack employee size data, either one of the outliers could be the one responsible for the modified results.

This study found that when controlling for number of employees, the effect of having two or more publications does not entirely go away, it was just less robust. Therefore, Hypothesis 3 is slightly supported because the effects do not completely cease to exist regardless of the type of sensitivity analyses performed.

LIMITATIONS AND IMPLICATIONS FOR FUTURE RESEARCH

The most obvious limitation of this study was the difficulty of collecting information on private companies. About 10% of orphan drug sponsors and 29% of non-orphan drug sponsors in my sample were public companies, and thus information on company size and the measures relating to my independent variables were more readily available. The lack of access to private company data, especially in regards to PRO formal ties, disabled this study from providing a complete analysis of the relationship

between an organization's public sector engagement and the likelihood of participating in the ODA. No conclusions could be drawn with respect to Hypothesis 2 due to the large number of missing cases for PRO formal ties. A valuable investigation for future investigation would be to address this hypothesis by devising alternative ways to gather information on company ties to PROs, aside from extracting information from SEC filings.

Another significant challenge was related to the independent variables. While these variables were selected as best representative of a firm's public sector engagement, there are other factors to consider which would provide an additional dimension to the study. Future research should therefore be directed at collecting different measures also related to public sector engagement, such as data on faculty founders. Faculty founders might influence ODA decisions because of their background in the academic sector; they may seek to make business decisions that emulate the goodwill norms associated with the academic setting. Also, as publishing is highly encouraged and often, required, for researchers in academics, these individuals will have gained a credible reputation which could further prompt faculty founders to seek to frame their biotechnology jobs as legitimate.

Another limitation was the sample size. Although I wish I could have studied a broader range of years, due to time and data constraints relating to the risk set definition, only organizations receiving their first orphan drug designation in the year of 2008 were able to be examined. Further studies would benefit from performing a comprehensive analysis of participating organizations over all years since the Act's enactment. Additionally, because I am interested in the factors that first initially lead an organization

to opt to develop an orphan drug, I chose to only study first-time sponsors. A future research endeavor that also examines recurring sponsors would shed light on the impetus driving an organization to continue to participate in the ODA.

Although some reasons have already been postulated, an additional worthwhile exploration for future research would be to divulge further into why the more sales a company has, the less the independent variables will matter. This finding is especially curious given the deduction that having more employees does not have an effect on the dependent variable. An explanation most certainly relates to economic factors; approaches relating to economic efficiency rather than to public engagement is likely to alter a firm's decision whether or not to develop an orphan drug. Furthermore, associated variables, such as the company already having produced a near-treatment, the firm's disease specialization, and the size of the patient population, would be necessary to collect as it would be useful in formulating market-based hypotheses for a future study.

CONCLUSION

This study draws attention to a prevalent issue of social justice: the reprehensible existence of health disparities that exist within our U.S health care system, specifically in regards to the lack of drugs and treatments for rare diseases. This disparity exists for organizational reasons. Understanding how legal interventions—specifically, the ODA—can be implemented in order to help stimulate these endeavors by altering the incentives of self-interested actors is an important step toward ensuring the development of drugs for markets that otherwise wouldn't have been served. My research concerns how public

sector engagement will cause a firm to react differently to a non-compulsory law by electing whether or not to follow the regulations.

A firm's connection to its institutional environment plays a vital role in its quest for organizational legitimacy. Public sector engagement can be measured in terms of NIH grants, formal ties to PROs, and publications. Results tentatively show that, as predicted, the closer a firm is to the public sphere, the greater the need to seek legitimacy as this characteristic carries a larger significance for its long-term survival. Therefore, results of my research provide a small amount of support for an institutional explanation for an organization's decision to participate in the ODA.

The results of this study have important implications for both policy makers, as well as for the segment of the population that are most directly affected—patients and families affected by rare diseases. The impact of institutional pressure on pharmaceutical and biotechnology organizations must be recognized and utilized in creating policies that will further encourage firms to take part in the ODA. For people with rare, orphan diseases, this legislation is vital to their livelihood and it is necessary for these stakeholders and other concerned parties to advocate for institutional participation. This study can help to promote research interest in the field of rare diseases by showing how developing an orphan drug can help organizations establish legitimacy in their institutional environment and thus, increase their chance of survival. Our society must remain committed to helping people with rare, orphan diseases and through continued dedication to this cause, we can truly make a difference in the fight for helping patients combat rare disease.

Figure 1. Number of Orphan Drug Designations Over Time (1983-2008)

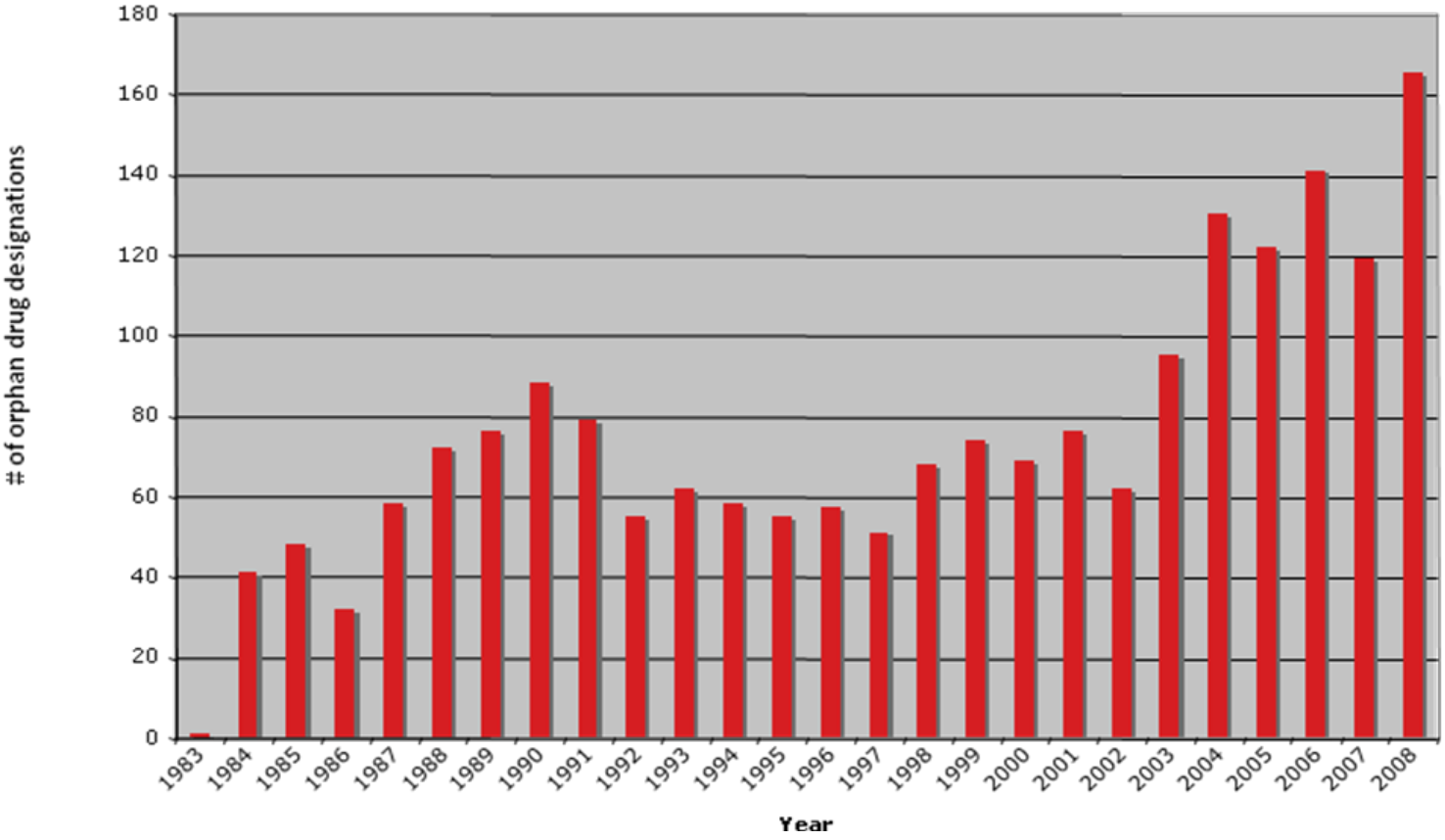

Figure 2. Histogram of Number of Publications for all firms

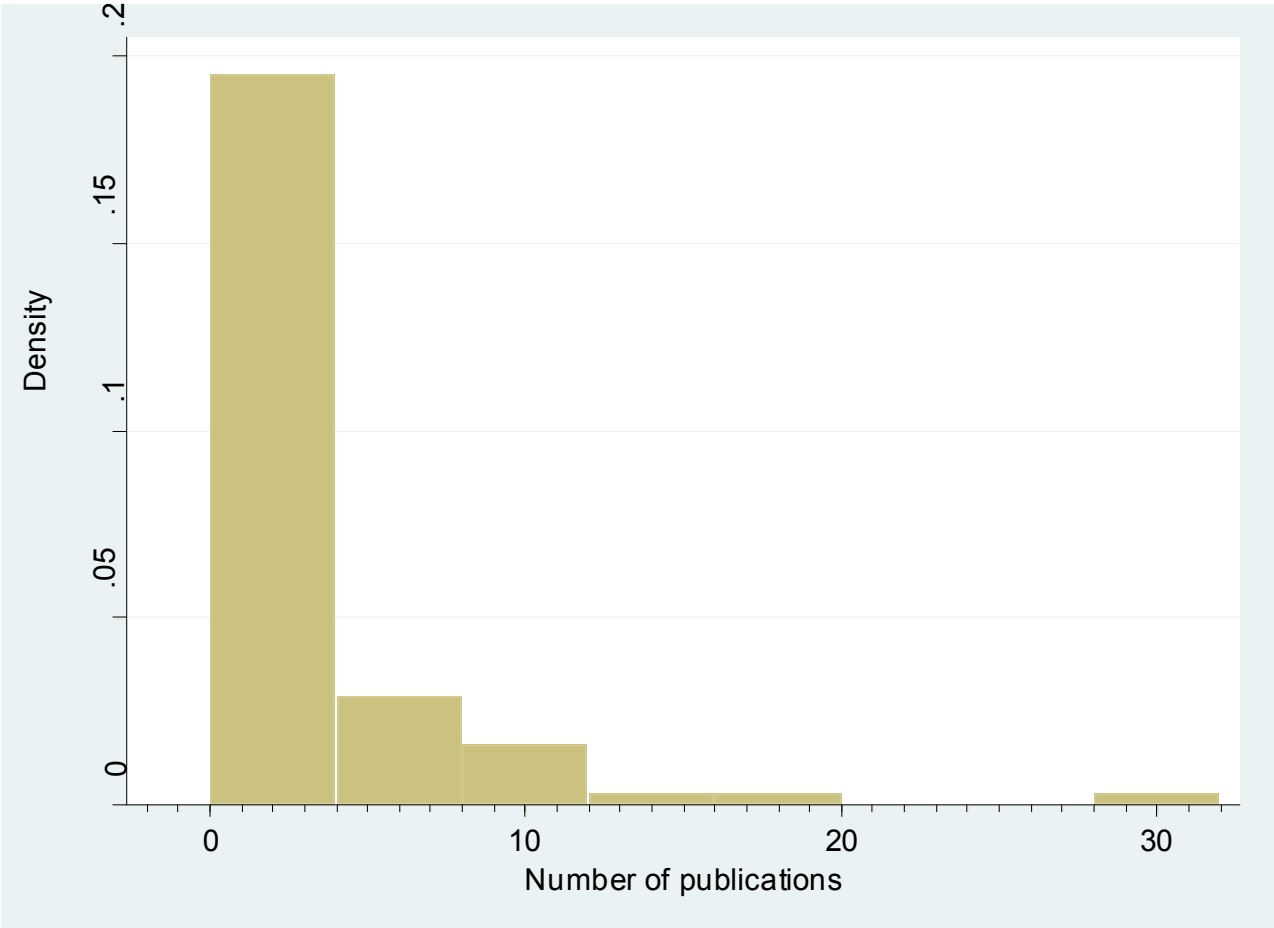

Table 1. Descriptive Statistics for Variables in the Analysis

Variable	Orphan Drug Sponsor				Non-Orphan Drug Sponsor			
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.
Founding Year	2001.8	4.603	1988	2007	1992.853	17.662	1923	2006
Number of Employees in 2008	20.222	40.406	3	212	1723.194	5105.287	3	24800
Annual Sales (millions) in 2008	6.700	9.857	0	41.8	636.815	1736.502	0.3	8050
Number of NIH Grants in 2006-2008	0.324	1.547	0	9	0.463	1.362	0	6
Number of ties to PROs in 2006-2008	1.778	1.856	0	5	0.714	1.437	0	5
Number of Publications in 2006-2008	2.811	5.995	0	32	1.854	3.883	0	19
N	37				41			

Table 2. Correlations

Variables	1	2	3	4	5	6
1. Age	1.000					
(N)	(64)					
2. Number of Employees in 2008	0.392	1.000				
(N)	(58)	(63)				
3. Annual Sales (millions) in 2008	0.382	0.976	1.000			
(N)	(40)	(42)	(44)			
4. Number of NIH Grants in 2006-2008	-0.035	-0.077	-0.075	1.000		
(N)	(64)	(63)	(44)	(78)		
5. Number of ties to PROs in 2006-2008	-0.394	-0.214	0.248	1.000		
(N)	(23)	(18)	(23)	(23)		
6. Number of Publications in 2006-2008	0.011	0.241	0.358	0.037	-0.149	1.000
(N)	(64)	(21)	(44)	(78)	(23)	(78)
		0.260				
		(63)				

Table 3. Logistic Coefficients for Regression Analysis of Sponsors of Orphan Drug Designations, 2008

	Model 1	Model 2	Model 3	Model 4	Model 5
Age (SE)	-0.090* (0.046)	-0.086* (0.046)	-0.092* (0.048)	-0.088* (0.049)	-0.088* (0.049)
Traded (SE)	-0.459 (0.764)	-0.636 (0.785)	-0.522 (0.790)	-0.875 (0.861)	-1.037 (0.887)
NIH Grant(s) (SE)		-1.532* (0.880)		-2.020* (0.978)	-0.745 (1.285)
Publication(s) (SE)			0.690 (0.585)	1.130* (0.673)	1.474* (0.763)
Interaction: NIH grant(s) X publication(s) (SE)					-2.209 (1.858)
Constant (SE)	0.790* (0.414)	1.011* (0.439)	0.581 (0.448)	0.745 (0.462)	0.692 (0.461)
Likelihood-ratio Chi-square	10.61*	14.13*	12.03*	17.22*	18.60*

Note: N=64

* $p \leq .05$ (one-tailed test)

Figure 3. Scatter Plot of NIH Grants and Publications with Outliers Identified

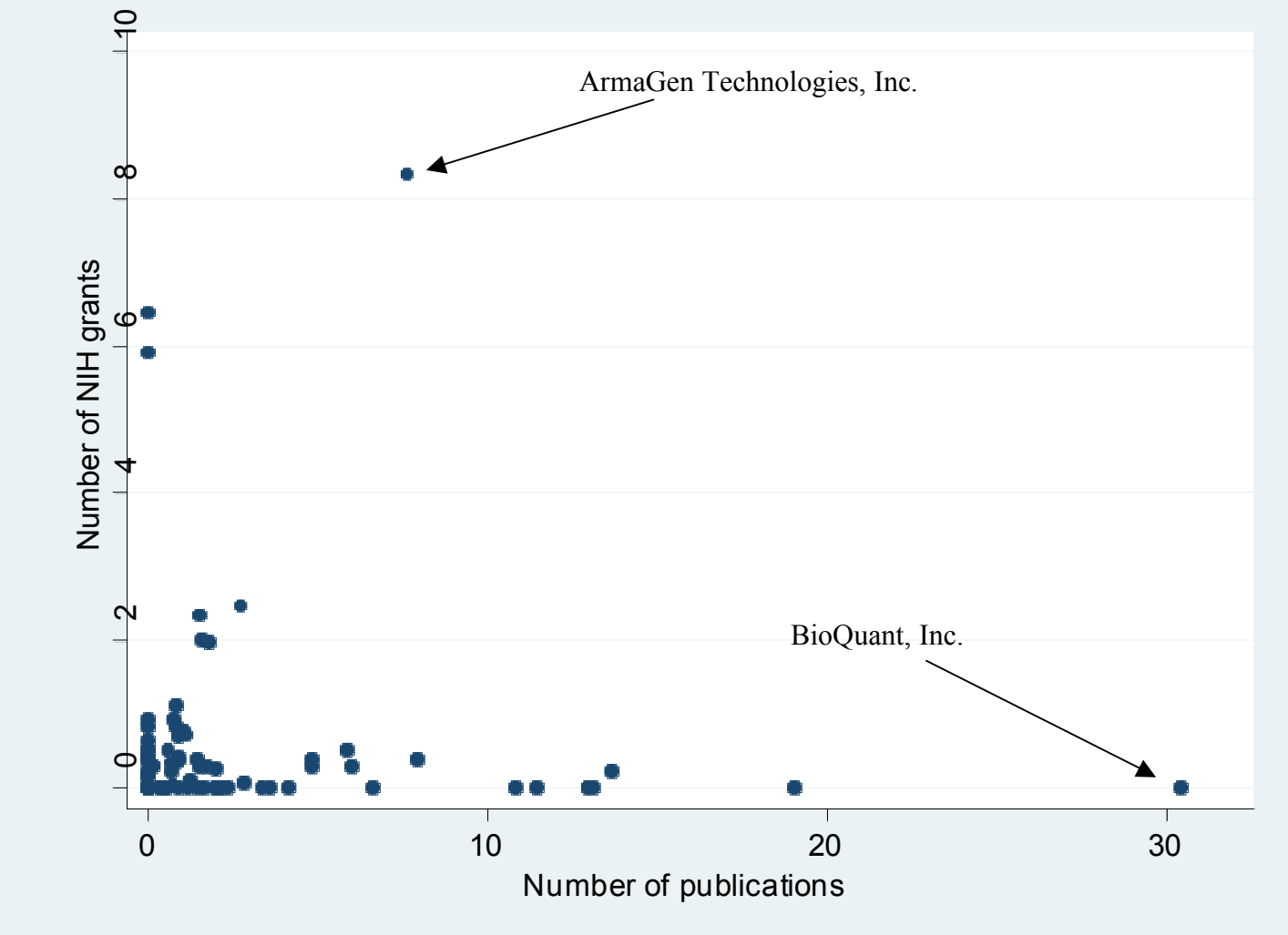

Table 4. Sensitivity Analysis—Variants of Table 3, Model 4

	Sensitivity to size variable (employees)		Sensitivity to size variable (sales)		Sensitivity to outliers		
	Including Variable	Sensitivity to missing size data	Including Variable	Sensitivity to missing size data	NIH grants	Publications	Both
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Number of Employees, 2008 (SE)	-0.014 (0.010)						
Annual Sales (in millions), 2008 (SE)			-0.0867* (0.042)				
Age (SE)	-0.031 (0.067)	-0.074 (0.048)	-0.051 (0.086)	-0.0898 (0.0584)	-0.0834* (0.0481)	-0.0895* (0.0492)	-0.085* (0.0486)
Traded (SE)	-0.105 (1.08)	-1.02 (0.898)	-1.094 (1.335)	-0.385 (0.930)	-0.874 (0.857)	-0.710 (0.863)	-0.795 (0.860)
NIH Grant(s) (SE)	-2.032* (1.02)	-1.811* (0.972)	-0.512 (1.475)	-1.228 (1.252)	-2.602* (1.202)	-1.938* (0.976)	-2.517* (1.199)
Publication(s) (SE)	1.400* (0.805)	0.869 (0.697)	1.926 (1.298)	0.326 (0.794)	1.044 (0.681)	1.035 (0.680)	0.942 (0.689)
Constant (SE)	0.571 (0.550)	0.644 (0.486)	1.354* (0.772)	0.655 (0.578)	0.735 (0.462)	0.742 (0.463)	0.733 (0.463)
Likelihood-ratio Chi-square	19.99*	13.83*	19.21*	7.95*	18.02*	16.30*	17.10*
N	58	58	40	40	63	63	62

* $p \leq .05$ (one-tailed test)

IV. REFERENCES

CRS Report for Congress. 2001. 13 Feb. 2009. <http://web.lexis-nexis.com.proxy.lib.umich.edu/congcomp/attachment/a.pdf?_m=9f0df3da2aca871fe297a8cd91ff1911&wchp=dGLbVzb-zSkSA&_md5=789952a06d4116d6b039cf8d04941661&ie=a.pdf>.

Dasgupta, Partha and Paul David. (1994). "Toward a New Economics of Science". *Research Policy* 23(5): 487-521.

Dimaggio, Paul & Walter W. Powell. "The Iron Cage Revisited: Institutional Isomorphism and Collective Rationality in Organizational Fields". *American Sociological Review*, 48(2), 147-160.

Dowling, John & Jeffrey Pfeffer. (1975). "Organizational Legitimacy: Social Values and Organizational Behavior". *The Pacific Sociological Review*, 18(1), 122-136. < http://www.jstor.org/pss/1388226>.

Edelman, Lauren B. & Mark C. Suchman. (1997). "The Legal Environments of Organizations". Annual Review of Sociology 23: 479.

Haffner, ME. (1999). "Orphan Drugs: The United States experience". *Drug Information Journal*, 33(2), 565-568.

Hogan, Janice Marchiafava. 1995. "Revamping the Orphan Drug Act: Potential Impact on the World Pharmaceutical Market". Law and Policy in International Business (26).

Meyer, John W. & Brian Rowan. (1977). "Institutional organizations: formal structure as myth and ceremony". *American Journal of Sociology*, 83, 340-63.

National Organization for Rare Disorders Website. 2009. "National Organization for Rare Disorders (NORD)". 11 Jan. 2010 <http://www.rarediseases.org/>.

Oliver, Christine. (1997). “Sustainable competitive advantage: Combining institutional and resource-based views”. *Strategic Management Journal*, 18(9), 697-713. <www.jstor.org/stable/3088134>. 18 Jan. 2010.

Owen-Smith, Jason & Walter W. Powell. (2005). "Accounting for Emergence and Novelty in Boston and Bay Area Biotechnology."Forthcoming in P. Braunerhjelm & M. Feldman (Eds.) Cluster Genesis: The Emergence of Technology Clusters and Their Implications for Government Policy. Cambridge, UK: Cambridge University Press.

Owen-Smith, Jason & Walter W. Powell. (2004). "Knowledge Networks as Channels and Conduits: The Effects of Spillovers in the Boston Biotechnology Community." *Organization Science.* 15(1):5-21.

Powell, Walter W. & Jason Owen-Smith. (1998) "Universities and the Market for Intellectual Property in the Life Sciences”. *Journal of Policy Analysis and Management*. 17(2): 253-277.

Sandel, Michael J. Justice: What’s the Right Thing to Do?. New York: Farrar, 2009.

United States. Congressional Budget Office (CBO). “Research and Development in the Pharmaceutical Industry”. Oct. 2006. 7 Jan. 2010 <http://www.cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf>.

United States. U.S. Department of Health and Human Services (HHS), Office of Inspector General. “The Orphan Drug Act: Implementation and Impact”. May 2001. 12 Feb. 2009. < http://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf>.

United States. U.S. Food and Drug Administration (FDA). “Basic Questions and

Answers About Clinical Trials". 16 Jul. 2009. 23 Jan. 2010. < http://www.fda.gov/ForConsumers/byAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm121345.htm>

United States. FDA. "Designating an Orphan Product: Drugs and Biologics". 28 Jul. 2009. 11 Jan. 2010. <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm>.

United States. FDA. "Developing Orphan Products: FDA and Rare Disease Day". 27 Feb. 2009. 7 Sep. 2009. <www.fda.gov/consumer/updates/oda020808>.

United States. FDA. "OOPD Program Overview". 12 Feb. 2009. <http://www.fda.gov/orphan/progovw.htm>.

United States. FDA. "Orphan Drug Act". 14 Oct. 2009. 11 Jan. 2010. <http://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/overview/ucm119477.htm>.

United States. FDA. "Orphan Drugs". 3 Mar. 2009. <http://www.fda.gov/cder/handbook/orphan.htm>.

United States. National Institute of Health (NIH). "Fact Sheet". 11 Jan. 2010. <http://www.nih.gov/about/researchresultsforthepublic/RareDiseasesCRN.pdf>.

Yin, Wesley. (2008). "Market incentives and pharmaceutical innovation". *Journal of Health Economics*, 27(4), 1060-1070.