Ownership vs. Contract: How Vertical Integration Affects Investment Decisions in Pharmaceutical R&D

Ilan Guedj[§]
MIT Sloan School of Management

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Abstract

This paper explores the effect of vertical integration on investment behavior in the pharmaceutical industry. I study a detailed, project-level sample of 4057 drug candidates that were sponsored by 40 large pharmaceutical firms during the period 1984-2001. Of these projects, 447 were conducted through a contractual alliance with another, smaller company that had discovered the drug candidate. The existence of these two types of governance structures allows me to compare integrated and non-integrated projects within the same firm. Controlling for project and firm characteristics, I document that pharmaceutical firms are more selective in continuing their integrated projects than in continuing projects governed by contract. I hypothesize that this difference is caused by the rigidity of the contract that governs non-integrated projects, making them less flexible in adapting to changes in the firm's situation. In line with this hypothesis, I document that although more frequently continued, non-integrated projects have a lower probability of success. Moreover, investment in non-integrated projects is less sensitive to the firm's cash flow and to the existence of other projects in the firm.

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[§]E52-442, 50 Memorial Drive, Cambridge, MA 02142. E-mail: guedj@mit.edu.

1 Introduction

How does vertical integration affect investment behavior and performance? I study this question by examining the project-level R&D investment decisions and performance of biopharmaceutical firms. I compare the investment of firms in their own projects with their investments in external alliances. Both types of investments seek to achieve the same goal – developing a new pharmaceutical drug – but in the former case the project is governed by outright ownership while in the latter case the project is governed by contract. Controlling for project and firm characteristics, I document that firms are more prone to terminate the projects they own than the ones they engage in through contractual alliances. This greater termination rate of the internal projects is not because they are worse on average than the alliance projects. In fact, the internal projects that are continued are more likely to succeed than the alliance projects. These findings are consistent with the view that firms use a higher continuation threshold on their internal projects than on their external projects.

This paper points to a critical difference between internal and external transactions. Understanding this difference is the central issue raised by Coase (1937) in his article "The Nature of the Firm." Coase raised two fundamental questions: What determines the boundaries of the firm? and, Do firm boundaries affect the allocation of resources? These questions have been the focus of a large body of theoretical research[1]. For the most part, however, the empirical literature – summarized in Whinston (2001) – addresses only the first of Coase's questions, by examining the causes of vertical integration. There is much less empirical research on the second issue, the effects of vertical integration. This paper contributes to this question by analyzing the effects of integration on the investment decisions regarding integrated

[1]Including the transaction cost approach of Williamson (1975, 1985) and Klein, Crawford and Alchian (1978); the property rights approach of Grossman and Hart (1986), Hart and Moore (1990), and Hart (1995); and the incentives-based models of Holmstrom and Milgrom (1991, 1994), Holmstrom and Tirole (1991), and Holmstrom (1999).

and non-integrated projects in the same firm.

I present a simple theoretical framework than can help to analyze the differences between internal (ownership-governed) projects and external (contract-governed) projects. The basic problem is as follows: An entrepreneur has an idea for a project; however, she is financially constrained. The entrepreneur signs a contractual alliance with a large and experienced firm, which can add value to the project and is willing to finance it. This is a multi-staged project where at each stage, some information is revealed and a decision, whether to continue investing or discontinue the project, needs to be made. The entrepreneur exerts effort to develop her idea, this effort is necessary for the success of the project.. The entrepreneur wants to guarantee that if the project is valuable to her, the firm will fund the project. If the firm decides not to fund the project, it will be very costly for the entrepreneur, as the entrepreneur will lose her private benefits associated with the continuation of her project. For example, cancellation of the project might send a negative signal about the value of her ideas, reducing the probability of the entrepreneur gaining financing for her other projects. These private benefits are quite useful to the financing firm, as they motivate the entrepreneur to exert effort; however, they can be the source of a conflict between the entrepreneur and the firm regarding continuation decisions.

Besides this alliance project, the firm also has an internal project, which it fully owns. The manager of this project is an employee of the firm. Since the manager does not need to have her project continued in order for her employer (the firm) to know the quality of her ideas, she enjoys few private benefits from the continuation of the project. Thus, the payment required to motivate the manager to exert effort is higher than the one required by an entrepreneur, who is partly self motivated by her private benefits. This is the basis of the main trade-off. On the one hand, it is more costly to motivate a manager who develops a project that she does not own than to motivate an entrepreneur who owns her project. However, the higher the entrepreneur's private benefits, the more the entrepreneur wants to guarantee that the project is continued. The result is that the firm is willing to agree to guarantee continuation of a project, even in some cases when the project has a negative NPV. This guarantee acts as an ex-ante incentive device for the entrepreneur. On the other hand, the advantage of an internally owned project is that the manager does not pressure the firm to continue her project as she does not own it, but at the same time, it is more costly to motivate her. The end result is that an entrepreneur will exert more effort than an internal manager, but the firm will be less selective about the quality of projects it is investing in compared to its own projects. This model highlights one value of ownership as being the flexibility the owner has with respect to investment decisions. However, it also shows that this flexibility comes at the cost of lost incentives.

Moreover, when the firm signs a contract with an entrepreneur, it binds itself ex ante. However, because the contract is incomplete, it cannot specify all the contingencies that would make continuation efficient. For example, some soft information may come in about market size, or about the success of the project, that can make the continuation of the project less promising. But the binding aspect of the project will make it very difficult for the firm to adjust its investment to changing situations in the future. Thus, when the firm finds itself constrained to cancel a project, it will elect to cancel an internal project. This means that internal projects will be more sensitive than external ones to changes in the firm's situation and opportunity set.

In order to test these empirical predictions, I perform an analysis using biopharmaceutical R&D project-level data. This setting is ideal for addressing this question for three reasons. First, there are two distinctive ownership structures for projects in the biopharmaceutical industry. Projects that are originated by the firm are fully owned and integrated, while at the same time, biopharmaceutical firms sign alliances with smaller and younger companies. These alliance projects, though financed by the firm, are owned by the originating company. These integrated and non-integrated projects co-exist in the same firm and in the same internal capital market. Second, there is a wealth of detailed, publicly-available information on project-level investments that these firms undertake, namely the clinical trials required by the U.S. Food and Drug Administration (FDA) in order to determine the safety and efficacy of drug candidates. Finally, the outcomes of these investments are measurable. Thus, one can compare, at a very detailed level, the investment behavior and performance of firms with respect to their different projects.

The biggest investments in this industry are the clinical trials that are required for a drug to be approved by the FDA[2]. A particular drug candidate must go through three phases of clinical trials on human subjects: small Phase I trials designed in most cases to test a drug's safety; larger Phase II trials to test both its safety and efficacy; and finally very large Phase III trials with as many as a several thousand subjects. At each point along the way, a company must decide based on scientific, clinical, and financial information whether to continue to the next, more expensive phase of clinical trials.

The empirical evidence in this study is consistent with the predictions of the model. Controlling for firm and project characteristics, alliance projects are 21% more likely to move from Phase I to Phase II, compared to internally integrated projects. However they are less likely to eventually succeed. The same projects are 20% less likely to move to the more expensive Phase III. Moreover, alliance projects that advance to Phase III are 10% less likely to succeed at getting an FDA approval. The results regarding these two measures of quality, advancing to Phase III and receiving FDA approval, show that the alliance projects that are advanced from Phase I to Phase II and from Phase II to Phase III are of lower quality.

Following the model, I investigate how these decisions depend on the firm's constraints. I find that the continuation decision with respect to integrated projects depends on the amount of cash available to the firm, the existence of other advanced

[2]The most recent estimate of the cost of getting a single drug approved is $802 million (deflated to 2000). This estimate factors in the expected costs associated with failed attempts to develop a drug.

projects in the firm, and, to a lesser extent, the existence of similar projects in the firm. Non-integrated projects are less sensitive than integrated projects to the firm's financial resources and to the existence of other advanced projects in which the firm could invest. However, they are sensitive to other similar projects in the firm. This seems to indicate not only that integrated and non-integrated projects are treated differently, but also that in such a functioning internal capital market, decisions regarding integrated projects follow a "winner picking" method, while non-integrated projects are ranked on a different scale.

These findings relate to two branches of the literature. The first is the literature on the effect vertical integration has on the firm's behavior. In order to address this question, one has to compare similar projects that only differ in their level of integration. Mullainathan and Scharfstein (2001) do so by making a comparison across firms. They compare the companies' decisions to hold more manufacturing capacity. Their results suggest a potential inefficient allocation of resources in that integrated firms seem to hold more manufacturing capacity when it is least needed. Berger, et al. (2004) use a different methodology. They compare the decisions of banks over time, before and after a merger that integrated previously separate activities. They show that non-integrated banks are better able to collect and act on soft information than large banks. This paper contributes to this literature by looking at the effect of vertical integration inside the same firm and comparing the decisions the same firm makes regarding different projects, when the difference is solely the level of integration of the project. An analysis inside the same firm is a cleaner experiment, since it allows a comparison of projects that are as similar as possible, thus isolating the investment decision from other factors that could affect it.

The second branch of literature this paper relates to is the internal and external capital markets literature. This literature has concentrated on the question of when an internal capital market adds or destroys value. Stein (1997) shows that integrating projects under one internal capital market can add value when headquarters has control rights that enable it to engage in "winner picking." Scharfstein and Stein (2000) show that rent-seeking behavior on the part of division managers can subvert the working of an internal capital market. In the spirit of Gertner, Scharfstein, and Stein (1994), this paper looks at the effect of integration on an internal capital market. Gertner, Scharfstein, and Stein (1994) develop an empirical model that shows that compared to bank financing, owner-provided financing reduces the employee's incentives while making it easier to efficiently redeploy assets. This paper shows that even in a functioning internal capital market, a distortion might arise due to a lack of full integration of certain projects.

The remainder of the paper proceeds as follows: in Section 2, I develop a simple model to structure the problem that arises when bringing a non-integrated project inside an internal capital market. In this section, I discuss the relevant empirical implications of the framework to the biopharmaceutical industry. Section 3 gives a short overview of alliances in the biopharmaceutical industry. Section 4 describes the data, and Section 5 presents the results. Section 6 concludes.

2 A Simple Model

This section outlines a simple model for comparing a firm's investment decisions with respect to a project when it is governed by outright ownership and when it is governed by a contract. Section 2.2 gives an interpretation the model in the context of biopharmaceutical development and develops the empirical implications of this framework.

The project has a life of two periods. At time $t = 0$ an investment I_0 is made. At time $t = 1$ uncertainty is resolved and the state of the world is observed. If the project is continued, an investment of I_1 is required. At time $t = 2$ the cash flows materialize. There are two states of the world, Good (G) or Bad (B). The ex ante probability of state G is θ and the ex ante probability of state B is $(1 - \theta)$. The probability θ depends on the manager's effort. The state of the world is observable and verifiable. If the state of the world is B, the expected cash flow at time 2 is zero, and thus the project is terminated at time 1. If the state of the world is G, there are two possible outcomes. With probability α, a cash flow X is realized, and with a probability of $(1-\alpha)$ no cash flow is realized. α can be seen as a measure of the quality of the project. α is random and can have one of two values, $\alpha \in \{\alpha_L, \alpha_H\}$, where $\alpha_H > \alpha_L$. The probability of $\alpha = \alpha_H$ is p, and the probability of $\alpha = \alpha_L$ is $(1-p)$. α is observable at time 1, but it is not verifiable and thus non-contractible. See Figure 3 for a timeline of the model.

The project is initiated by a manager who is key to the development of the project. Thus, the manager needs to exert effort between time 0 and 1 in order to affect the probability of getting to the good state of the world. The project manager receives a payment w at time 2 if the project is successful. The manager chooses a level of effort, θ, which increases the probability that the project is successful. However, the manager incurs a personal, non-pecuniary cost, $\frac{1}{2}\beta\theta^2$, in doing so, where $\beta > 0$. This effort choice cannot be observed by anyone and thus contracts cannot be made contingent on it. It is also assumed that the manager has a "personal gain," b, if her project is continued at time 1, even if the project generates no cash flow at time 2. For example, b could be thought of as a shock to the manager's reputation, affecting the value of her other projects that share the same technology.

I will use this personal gain or externality, b, to differentiate between internal and external projects. When a project is internal, the manager has a low personal gain from the project. However, when the manager *owns* the project she has a high personal gain. When this personal gain is viewed as the externality received due to the information about the general value of the manager's projects, it is clear that if the manager does not own the project she does not gain much from that externality. Since the firm can observe the state of the world and the real value of the project, it doesn't need to continue a project in order to value the work of the manager. However, when the manager owns the project, the informational value of continuation can be quite high, for example, if the manager owns a start-up company with two projects, one being developed and the other one needs funding. By having the first project continued, a positive signal would be sent to the market about the potential value of the second project, increasing the probability of securing funding for that project.

Regardless of the ownership of the project, it is assumed that the manager is risk neutral and does not finance the project outside of the firm. In the case of an independent entrepreneur, this model concentrates on the situation where the financially constrained entrepreneur has elected to develop the project in alliance with the firm. In order to simplify the analysis, it is assumed that, if possible, the manager prefers to have her project financed by the firm.

There are several potential investment decisions the firm can make. The firm can elect to always invest at time 1, to invest only if the state of the world is G, or only if the state of the world is G and the realization of the quality of the project is $\alpha = \alpha_H$. Given the that the state of the world is observable and contractible, the firm will not invest if the state of the world is B. However, if the state of the world is G, it can always invest or only if $\alpha = \alpha_H$. Since α is non-contractible, in this case the contract must be set up so that it is in the interest of the firm ex post to make an investment of I_1 only when α turns out to be α_H. By contrast, if the contract calls for the firm to always invest in state G regardless of α, the payments do not need to insure that it is ex post optimal for the firm to invest regardless of α.

In general, the contract can specify payments at time 0, time 1 conditional on G or B. It can be shown that the optimal compensation is at time 2 conditional on success as it fully aligns the manager's incentives with the firm's objective function. Therefore, the firm can offer two different payments dependent on whether it plans to always invest at time 1 or only if the realization of the quality of the project at time 1 is $\alpha = \alpha_H$.

2.1 Contracts

2.1.1 Contract 1 - Invest only if $\alpha = \alpha_H$

This contract stipulates that at time 1, the firm will invest in the project only if it observes that the state of the world is G and that the probability of a non-zero cash flow at time 2 is α_H. Thus, the firm will choose a payment w_H such that:

$$\max_{w_H} E[\pi^{Firm}] = E[\theta_H^*(\alpha(X - w_H) - I_1) - I_0 \mid \alpha = \alpha_H] \tag{1}$$

subject to

$$\theta_H^* \in \arg\max_{\theta_H} E[U(\pi^{Manager})] = E[\theta_H(\alpha w_H + b) - \frac{1}{2}\beta\theta^2 \mid \alpha = \alpha_H] \tag{ICC}$$

$$E[U(\pi^{Manager})] = E[\theta_H(\alpha w_H + b) - \frac{1}{2}\beta\theta^2 \mid \alpha = \alpha_H] \geq 0 \tag{IRC}$$

Therefore, the manager will optimize her effort level given the payment w_H and the firm will optimize the payment in order to increase the effort level θ_H. The result is:

$$\theta_H^* = \frac{p(\alpha_H X - I_1 + b)}{2\beta} \tag{2}$$

$$w_H^* = \frac{\alpha_H X - I_1 - b}{2\alpha_H} \tag{3}$$

The payment w_H^* meets the feasibility constraint:

$$w_H^* \leq X - \frac{I_1}{\alpha_H}$$

As one can see in equation (2), the manager's effort increases with b. The more the manager gains from the continuation of the project at time 1, the more the manager will exert effort in order to reach the state G and increase the probability of continuation. However, as equation (3) implies, the higher b is, the lower the payment w needs to be for the principal to induce the manager to exert the same level of effort. This is the basic insight of this model. When a manager owns her project, a lower remuneration is needed in order to induce exertion of effort by the manager. However, when a manager who needs to exert effort for the success of the project does not own the project, the principal needs to pay a higher payment in order to induce the manager to exert effort.

2.1.2 Contract 2 - Always Invest

This contract stipulates that at time 1, the firm will invest in the project regardless of the realization α as long as the state of the world is G. Thus, the firm will choose a payment w_L such that:

$$\max_{w_L} \; E[\pi^{Firm}] = E[\theta_L^*(\alpha(X - w_L) - I_1) - I_0] \tag{1b}$$

subject to

$$\theta_L^* \in \arg\max_{\theta_L} \; E[U(\pi^{Manager})] = E[\theta_L(\alpha w_L + b) - \frac{1}{2}\beta\theta^2] \tag{ICC}$$

$$E[U(\pi^{Manager})] = E[\theta_L(\alpha w_L + b) - \frac{1}{2}\beta\theta^2] \geq 0 \tag{IRC}$$

Therefore, the manager will optimize her effort level given the payment w_L and the firm will optimize the payment in order to increase the effort level θ_L. The result is:

$$\theta_L^* = \frac{\overline{\alpha}X - I_1 + b}{2\beta} \tag{2b}$$

$$w_L^* = \frac{\overline{\alpha}X - I_1 - b}{2\overline{\alpha}} \tag{3b}$$

where $\overline{\alpha} = p\alpha_H + (1-p)\alpha_L$. The payment w_H^* meets the feasibility constraint:

$$w_L^* \leq X - \frac{I_1}{\overline{\alpha}}$$

The basic results from the first contract hold in the same way with this contract. The effort level θ_L increases with b and the manager's payment decreases with b.

2.1.3 Which Contract Will be Preferred?

The second contract will be chosen if:

1) $E[\pi^{Firm}|\ contract\ 2] \geq E[\pi^{Firm}|\ contract\ 1]$ and

2) $E[\pi^{Manager}|\ contract\ 2] \geq E[\pi^{Manager}|\ contract\ 1]$.

This will happen if:

$$b \geq I_1 - \alpha_L X \tag{4}$$

If the second contract is chosen, the effort the manager will exert θ_H will be higher than the effort the manager would exert in case of the first contract θ_L:

$$\theta_H - \theta_L = \frac{(1-p)(\alpha_L X - I_1 + b)}{2\beta} \tag{5}$$

which is always positive if the second contract is preferred.

The second contract will be chosen regardless of b if the project has a positive NPV even when $\alpha = \alpha_L$ (i.e., when $\alpha_L X - I_1 > 0$). However, when the project has a negative NPV when $\alpha = \alpha_L$, the decision of which contract to choose depends on how large b is. If b is large enough, even projects with very negative NPVs will be developed at time 1. This situation is solely due to the existence of this external gain for the manager that allows in a sense to the firm to extract some of this gain by lowering the manager's payment.

2.2 Empirical Implications

This simple model generates several empirical implications regarding the investment decision of the firm when it has both integrated and non-integrated projects. This section develops the empirical implications in the context of the biopharmaceutical industry. In the context of the biopharmaceutical industry, the timeline of the model would be equivalent to engaging in Phase I (at time 0), deciding to move to Phase II (at time 1), and getting FDA approval (at time 2). α is the equivalent of the conditional probability of receiving FDA approval given that the project advanced to Phase II.

Prediction 1 *All else equal, the probability of a project advancing from Phase I to Phase II will be higher for a non-integrated (alliance) project than for an integrated (internal) project.*

Regardless of the chosen contract, the effort level exerted by the manager increases with b:

$$\frac{\partial\, \theta^*}{\partial\, b} > 0$$

Moreover, when $b \geq I_1 - \alpha_L X$, the second contract will be chosen for non-integrated projects, while the first contract will be chosen for integrated projects. In such a case, as equation (5) shows, the effort level will be higher since $\theta_H > \theta_L$.

Prediction 2 *Non-integrated projects will have ex post a lower success rate than integrated projects.*

When $b \geq I_1 - \alpha_L X$ the second contract will be chosen for alliance projects. The firm will always invest in those projects at Phase II. Due to that, the average probability of success of such projects will be equal to $\overline{\alpha} = p\alpha_H + (1-p)\alpha_L$. However, internal projects will always have the first form of contract, resulting in a probability of success equal to α_H. The higher b, the greater the probability that a project with $\alpha = \alpha_L$ will be undertaken. The result is that cross sectionally, the average quality of an alliance project (its α) will be lower than the average quality of an internal project, since alliance projects will have a lower cutoff for continuation.

Prediction 3 *The firm's investment decisions regarding integrated projects compared to non-integrated projects will be more sensitive to financial and human capital constraints, and will be more sensitive to the existence of other projects in the firm's portfolio.*

The firm and the external entrepreneur have a binding contract. Until now I have assumed that all the agreement are not open for renegotiation. The agreement between the firm and its employee can be seen as somewhat different. This is not a contract per se but an agreement where the firm commits to pay a certain payment. If the firm chooses so, it could pay the payment w_H and yet not continue a project, for example if it is financially constrained. This flexibility, is another aspect of ownership. As defined by Grossman and Hart (1986) this is one of the prerogative of the owner, to have the control on any aspect that has not been given away in a contract. The agreement between the owner and the employee does not stipulate continuation but rather a certain wage in which it is in the interest of the firm ex post to make that investment. However, if the firm's interest are altered, as the rightful owner, it has the flexibility not to invest.

3 The Pharmaceutical Industry and Alliances - Background

In this study I restrict my attention to the R&D of drug development in the pharmaceutical industry. There are a few reasons for this. First, due to regulation, detailed data is available on project level decisions. Second, it is possible to compare different projects inside the same firm, and across firms, since all drug development projects have to follow the same stages and procedures. This creates a relative homogeneity in the comparison of projects. Third, the outcomes of projects are measurable and comparable. A successful project is one that receives FDA approval. Fourth, there exists much heterogeneity in ownership structures of projects in this industry. Fifth, the biopharmaceutical industry is a major industry in R&D expenditure. In 2000, it accounted for 25% of all expenditure on R&D in the US.

This section gives a brief background on the industry and the mechanics of alliances.

3.1 The Drug Development Process

After a drug compound has been identified through pre-clinical research, the biggest investments that biopharmaceutical firms make are the clinical trials they conduct to prove the safety and efficacy of the drug candidate. In order to gain regulatory approval for market introduction, the FDA requires that biopharmaceutical companies provide substantial evidence of a drug's effectiveness through adequate and well-controlled clinical investigations. Proof of the drug's effectiveness must be provided by the results of randomized controlled trials. These are comprised of three main rounds of clinical trials on human subjects.

Phase I trials are typically conducted on fewer than 30 patients and are designed to determine a drug's safety. For most diseases, these trials are performed with healthy subjects. DiMasi, et. al. (2003), using a sample of 68 drug candidates undergoing trials at large biopharmaceutical firms between 1983 and 1994, estimate that the mean (median) out-of-pocket cost of a Phase I trial was $15.2 million ($13.9 million) deflated to year 2000 US Dollar terms.

Phase II trials are larger and more costly than Phase I trials. They are conducted on as many as a few hundred subjects, use patients with the disease, and are designed to test both the safety and efficacy of the drug agent. The mean (median) cost of a Phase II trial in the DiMasi, et. al. sample was $23.5 million ($17.0 million).

Finally, Phase III trials are typically very large studies, including possibly thousands of subjects. The mean (median) cost of a Phase III trial in the sample was $86.3 million ($62.0 million). After completing these trials, a drug sponsor can seek regulatory approval from the FDA by filing a New Drug Application (NDA).

3.2 Alliances

Alliances are a common way for pharmaceutical firms to augment their drug pipeline; they can be signed at any stage in the drug development process. Alliances signed at an early stage (preclinical) are usually longer-term relationships. The main aspect is the financing of the entire process. These alliances usually have a broad scope and include most of the applications of an underlying technology. Alliances signed at mid stage (during clinical trials) are somewhat different. The disease the drug is supposed to cure is more defined and therefore the deal typically is narrower in scope. The rationale behind late stage alliances has less to do with financing (as most of the cost has already been incurred) and more to do with utilizing the marketing capabilities of large pharmaceutical firms.

Figure 1 gives the distribution of alliances over time by the stage of signing. As one can see, the number of alliances has increased over time. Large biopharmaceutical firms are relying more on these alliances to supplement their own pipeline. Figure 2 details the alliance total cost by stages.

There are many ways to structure alliances. In general, however, most alliances have the same components. Most pre-commercial payments to licensors can be allocated to one or more of four categories: (1) upfront or licensing fees; (2) R&D payments; (3) milestone payments; and (4) equity[3]. Average upfront payments tend to be larger the more advanced the stage of the alliance at signing (this is a way to participate in the prior cost of research and development incurred by the licensor). For clinical-stage alliances, R&D payments usually depend on the development of the next generation or back-up compounds. "Milestone" is a general definition of all event-contingent payments, including achievement of benchmarks associated with a compound's early or clinical development through first commercial sale, as well as patent issuance. Equity is one of the less common components of an alliance, as many do not include an equity investment.

Although each alliance is structured differently, the components are similar. However, alliances differ a lot depending on the stage at which they were signed. Therefore, in this paper I will concentrate only on early-stage alliances in order to reduce the variability of the different contracts and the effect it could have on the outcome of

[3]See Lerner and Malmendier (2004) for a thorough analysis of alliance contracts.

the drug development process.

4 Data

4.1 Data Source

The main data used in this study is obtained from PJB Publications' *PharmaProjects*. The PharmaProjects is a UK based commercial database that tracks drug compounds through their stages of development, from as early as pre-clinical laboratory studies to FDA approval. This database is typically licensed by major pharmaceutical, biotech, accounting, and law firms for the purpose of learning what the competition is doing. Since clinical trials are performed by medical institutions that publish the results of their research, the PharmaProjects is able to gather information on projects of both public and private companies. In addition to identifying the drug and its sponsoring organization, the PharmaProjects also gives information on the timeline of development (including the dates of Phase I, Phase II, Phase III, and FDA approval or discontinuation of the project). This database also provides detailed information on the drug candidates, including the indication it is aimed to cure, its pharmacological routes, its potential market value and of course the sponsoring firm. This data not only allows tracking of drug candidates over time, it also allows building a time series of each firm's R&D portfolio and its pipeline of drugs.

Data on the alliances is obtained from the databases of Recombinant Capital (ReCap), a San Francisco-based consulting firm specializing in tracking the biopharmaceutical industry, and mostly the alliances between the companies in this industry. As mentioned earlier, one advantage of studying biopharmaceutical firms is the degree of disclosure in this industry. Publicly traded biopharmaceutical firms, like other concerns, are required by the US Securities and Exchange Commission (SEC) to file material documents. Biopharmaceutical companies tend to interpret this requirement conservatively, and often file alliance contracts. This allows ReCap to gather information about alliance contracts between various biopharmaceutical companies even if one of them is a private company.

4.2 Data Sample

The empirical design of this study requires concentrating on firms that have both internally and externally developed projects. For this purpose, I concentrate on the 40 largest public biopharmaceutical firms. I focus only on public firms for two main reasons. The quality of information should be equivalent since they have to follow the same disclosure rules. It also allows me to link the drug development data to financial information from COMPUSTAT.

I extract from PharmaProjects all the drug development projects data that involves any of those 40 firms and that have valid information. This results in 3610 projects initiated by 40 companies between the years 1984-2001. I do not gather information on projects initiated after the year 2001 so as to have enough time to get information on movement to phase II.

I also extract from ReCap information on projects where there was an alliance that involved one of these 40 companies as the financing side of the alliance. I manually match these alliances with projects in PharmaProjects using the drug name, the originator's name and the start-up's name. In this study I concentrated on alliances signed before phase I. In particular, I eliminate alliances where:

- One of the parties is a university, medical center, non-profit organization, or government agency.
- One of the parties has a controlling interest in the other, either through a majority equity stake or through a purchase option (e.g., an alliance between a firm and one of its R&D limited partnerships).
- More than two firms are involved, making the analysis less clean and tractable.

- The agreement as filed contains no information on the stage it which it was signed.
- The alliance was signed after phase I had been initiated. The later the stage, the less the alliance is about research and development, and the more it is about combining marketing or manufacturing capabilities.

This results in 447 drug candidates. I will refer to projects originated by a firm as *internal* and those that were originated by another company and the firm signed an alliance on as an *external* project. All this results in 4057 drug development projects, of which 3610 were internally developed and 447 were externally developed.

4.3 Summary Statistics

4.3.1 Information on Clinical Trials

The main focus of my analysis is the decision a firm makes whether (and when) to advance a project from one phase to another. Table 1 Panel A reports the number of projects and the percentage of projects in each phase. Table 1 Panel B reports the distribution of the time between different phases. Since it takes some time to start a new clinical phase, in the cases where the time to Phase II is less than one year, it indicates that some or even all the preparations were undertaken before Phase I was finished. This implies that the decision was taken with no real regard to the clinical data generated by Phase I. As table 1 Panel B indicates, the average time from the beginning of a Phase I trial to the beginning of the first Phase II trial is 1.79 years. The mean time from Phase II to Phase III is 2.4 years. These results are similar to the results in DiMasi et. al. (2003).

Of course, not all trials move forward to the next phase. As table 1 Panel A shows, only 71% of the internally developed projects advance from the pre-clinical stage to Phase I. The figure regarding alliance projects is quite different, 93% of them advance to Phase I. However, this is not surprising. This is not an unbiased sample of all pre-clinical projects developed by startups. This is the subset of those projects that generated enough interest for a large biopharmaceutical company to sign an alliance on. It is not unreasonable to expect that such an agreement is signed with the intent to advance to clinical trial. A caveat that must be noted is that since the most reliable source of information about drugs for *PharmaProjects* is clinical trial result, it is possible that if a drug was developed by a small private company that never reached clinical trial it may not have been recorded. In such a case there would have been no way to match it to an alliance agreement if one were available. Due to all that, I will not look at the decision to advance to Phase I, but only at the subsequent decisions that do not have those potential problems.

The other transition probabilities indicate the main results of this study. Internal projects advance to Phase II with a probability of 70%, while external projects advance with a probability of 75%. They also do so at a much higher pace: 1.57 years compared to 1.80 years. However, in the probability of advancing to Phase III the order is reversed. Internal projects have a probability of 54% while external projects advance only with a probability of 45%. The probability of success of an internal project from Phase I to FDA approval is 22% while external project have a success rate of 17%, even they got more chances by advancing to Phase II in higher numbers.

4.3.2 Control Variables

The analysis controls for important characteristics of the drugs in development.

Table 2 reports the distribution of therapeutic classes across the different compounds. A therapeutic class is the main disease the drug is aiming at. The therapeutic activity codes are as defined in the Pharmaprojects Therapeutic Classification System (PTCS). This classification is based on the original classification devised by the European Pharmaceutical Market Research Association (EPhMRA). The PTCS is divided into fourteen major sections covering broad therapeutic areas, such as blood and clotting products, anticancer agents or respiratory agents. This classification is similar to the World Health Organization's (WHO) typology used by Danzon, Nicholson, and Pereira (2003). As Danzon et. al. have shown, different therapeutic classes carry different probabilities of success; it is thus important to control for those differences. As one can see in table 2, there is a wide dispersion between internal and external. Some of the smaller indications do not have alliance projects, mostly indicating that these indications either require some unique expertise, or that the cost cannot support the creation of a new company. In general, one can observe that firms use alliances in most of the indications they develop drugs for, making it a widely used tool for enhancing their pipeline.

Different compounds that aim at different diseases may also differ in their potential financial value. Table 3 Panel A reports the distribution of the estimated potential market size of each compound if eventually approved. These figures are estimated by the PharmaProjects. There doesn't seem to be a large difference in project types between alliance and internal projects.

In order to control for the novelty of the compound I use the pharmacology of a drug as described by Guedj and Scharfstein (2004). The pharmacology describes a drug's mechanism of action in the body, through which it exerts its therapeutic effect, i.e. it identifies the biological agent or process the drug stimulates or inhibits. The novelty ranking is based on the chronological use of a pharmacological mechanism for a certain therapeutic class. Using the entire universe of compounds developed in the past 20 years (both approved and discontinued compounds), I rank each compound by the chronological appearance of its pharmacological mechanism and therapeutic class. For example, compound A uses the mechanism "Phosphodiesterase V inhibitor" and its development started in 1990, and compound B uses the same mechanism, but its development started in 1991. Then, compound A will receive the rank 1 and compound B will receive a rank of 2 and so on. This methodology gives a basic sense of whether a compound uses a mechanism that is new or that has been previously used. Table 3 Panel B describes of mean comparison of novelty of drugs between internal and alliance projects. The mean rank of a drug developed by an early stage drug is 24.07. While the mean rank of a drug developed by a mature company is 28.31. The difference is not statistically significant.

4.3.3 Information on Companies

Table 4 presents summary data (deflated to the year 2000 US Dollar terms) on the public companies sponsoring the trials in the sample. On average, the public companies are very large, with mean revenues of over $9 billion, mean assets of almost $13 billion, mean cash of close to $2.2 billion and mean R&D of about $1 billion. The average market capitalization is over $32 billion and the mean Q is 3.45. Nonetheless, there is wide heterogeneity among the firms in the sample. This is mainly due to the long time series, whereas most of the companies have grown over time to the large size as indicated by the means. Some of the largest companies in the sample, are the largest world drug manufacturers. With sales of more that $35 billion, R&D expenditure of almost $3 billion and more than 100 thousand employees worldwide.

5 Empirical Analysis

In this section I compare the investment decisions firms make regarding projects that are vertically integrated (internal projects) and projects that are not integrated (external or alliance projects) but that are governed by a contract.

5.1 Basic Analysis

5.1.1 Phase I to Phase II Transition Probabilities

All the projects in this analysis were either developed inside the firm from the earliest stages (pre-clinical) or an alliance contract was signed prior to the beginning of Phase I. However, it is reasonable to assume that if a contract was signed prior to Phase I, there might have been an ex ante intent to move to Phase I. Due to this possibility, in this work I will not concentrate on the decision to advance to Phase I, but rather on the decision of whether to move to Phase II given that Phase I was completed. As mentioned in section 4, Phase II is a large and expensive phase with a mean cost of $23.5 million. Often, more than one Phase II is required, making it even more expensive. Therefore, due to its potential cost, the decision to move from Phase I to Phase II is an ideal setting to address the question of whether ownership has an effect on the investment decisions of the firm.

The following analysis looks at the factors that affect whether a firm advances a drug from Phase I to Phase II. This is aimed at testing Prediction 1 from section 2.2. The hypothesis of this prediction is that firms will be more likely to terminate an internal project than an alliance project. All the tables reported are of a linear probability estimation.

I do not estimate Probit models, because Maximum likelihood estimators in the presence of fixed effects suffer from the 'incidental parameter problem' as was first analyzed by Neyman and Scott (1948). There is a vast literature such as Heckman (1981) who shows that in a Probit regression with a small sample, the presence of fixed effects might generate an upward bias in the estimation of β. This upward bias is exacerbated the smaller the sample is compared to the number of fixed effects. Although this sample is quite large, I report a linear model in order to have consistent estimates. The results also hold very similarly when using a Probit model and when using a Conditional Probit Model as suggested by Chamberlain (1980) and a Cox proportional hazard model.

In table 5, I report the results of the estimation of the probability of moving from Phase I to Phase II within two years. I use a two year cutoff on Phase II decisions for two main reasons. First, without a cutoff, Phase I trials that were begun in the early part of the sample would be more likely to be taken forward. If there is an over-representation of one type of ownership structure in the early period, this would bias the findings. The second reason to use a time cutoff is to measure the aggressiveness with which firms move forward in the clinical trials process. As one can see in table 1, the mean time to move from Phase I to Phase II is 1.69 years and the median is 1.82 years. To avoid making seemingly arbitrary cutoffs, a Cox proportional hazard model has been estimated (not reported) and yields similar results. The results are robust to using different time cutoffs, for example Table 6 reports results using a 3 year cutoff.

Therefore, the dependent variable gets the value of 1 if the drug moved to Phase II within two years of initiating Phase I and zero otherwise. The independent variables include a variable External that gets a value of 1 if the project was originated by another company and is developed under a contract, and gets zero if it is an internal project. The first column of Table 5 is a simple comparison of means. An alliance project has a probability of moving from Phase I to Phase II in two years that is higher by 15.9% than an internal project. All the t-statistics in the table are based on robust standard errors corrected for firm-level clustering.

One potential explanation for this result is that alliance projects are inherently different. Those projects are developed by young start-up companies. For an entrepreneur to start a start-up and receive venture funding, the idea behind the start-up must have a high potential value. Moreover, one could speculate that the idea should be original and novel enough to have a potential for competing with products from well established firms. Therefore, one could reasonably hypothesize that alliance projects are more novel and therefore it is not unreasonable for those companies to be more aggressive regarding their decision to advance from Phase I to Phase II. Column 2 of Table 5 adds a measure of novelty. The novelty variable assesses whether the technology of the drug is new in treating that specific disease. It is constructed by looking at all the compounds developed over time and their pharmacological description (their mechanism of action). Each compound is ranked chronologically by the group of compounds that use the same pharmacology for the same therapeutic class. This control does not change the basic result, yet shows that indeed more novel drugs will have a higher propensity to move to Phase II. Those start-ups are usually generically referred to as 'Biotech' since a large majority of them use a biologic source (as opposed to a chemical source) for their compounds. Since biologic and chemical compounds could be different, column 3 adds a dummy for whether the compound is of biologic source. Since biologic compounds are relatively new, this adds another measure of novelty.

A second possible explanation for this finding could be that drugs developed by start-ups aim at higher payoff markets (increasing Y_i in the model). Column 4 adds controls for the potential market size. The *PharmaProjects* estimates the potential market size of a drug. From this assessment I generate three dummies for Small, Medium, and Large market size (0-2$b, 2-5$b, and +5$b respectively). The Large and Small dummies are added to the regression. Drug candidates with higher potential payoffs have a higher propensity to move to Phase II, however, this doesn't hinder on the basic result that alliance projects are more likely to move to Phase II.

In order to control for other potential explanations for this result I add three sets of fixed effects: firm fixed-effects, therapeutic class fixed-effects, and year fixed-effects. Company fixed effects are added in column 5. Different companies may have different policies and different degrees of aggressiveness in pursuing clinical trials. I add therapeutic class fixed-effects since different diseases carry different probabilities of success (see for example Danzon, Nicholson, and Pereira (2003) for an analysis of success probability by therapeutic class). Column 6 gives the results of the analysis with therapeutic fixed effects, not materially altering the result. Year fixed effects are added in column 5. As argued by Lerner, Shane, and Tsai (2003), in different years there are different market conditions that may lead to renegotiations of alliance contracts or cancellations of those contracts.

Column 7 summarizes the results including all the controls and fixed effects. The estimated marginal effect of an alliance is 0.2104, indicating that an alliance project is 21% more likely than an internal project to move forward from Phase I to Phase II. Table 6 reports the results of the same regression but with a dependent variable that uses a cutoff of 3 years. As one can see, the results are very similar, indicating that the results are not due to the fact that alliance projects are developed faster.

5.1.2 Performance of the Projects that Advanced to Phase II

As Prediction 2 suggests, non-integrated projects should have a higher probability of advancing from Phase I to Phase II, but the eventual success of these projects should be lower than the success of integrated projects. I use two measures for the probability of success of the projects: the probability of moving from Phase II to Phase III, and the actual approval of the drug by the FDA.

There are several reasons I use the decision to advance from Phase II to Phase III as a measure of success although it is a choice the firm makes. First, the mean cost of a Phase III is estimated at $86.3 million, but the actual cost can escalate to hundreds of millions of dollars depending on the therapeutic class and the number of times it needs to be undertaken. Most Phase clinical trials III are done more than once and in different countries in order to receive regulatory approval from each separate country. This high cost reduces the incentive of a firm to advance a low quality compound. Second, as shown by Guedj and Scharfstein (2004), the decision to advance from Phase II to Phase III is closely linked to clinical results at Phase II. This makes this decision a good proxy for the quality of a compound. However, since FDA approval is the ultimate measure of success of any drug development project, I will use it as a second measure of quality.

Table 7 reports the results of the regression of the probability of advancing from Phase II to Phase III within three years, given that the drug candidate was in Phase II. Similarly to the Phase II analysis, I use a three-year time cutoff on Phase III decisions. The results are robust to different time cutoffs and to a non reported Cox proportional hazard model analysis. Column 1 is a simple comparison of means. An alliance project that advanced to Phase II has about 9% less chances to advance to Phase III. The other columns represent the regression of this probability on the same controls that were described in section 5.1.1. Controlling for the novelty of the drug has quite a strong effect. More novel drugs have a 15% higher probability of advancing to the next phase just due to their novelty. At that stage the potential market size does not seem to play a large role in the firm's decision. However, adding the therapeutic class fixed effects makes a dramatic change. As mentioned earlier, different diseases carry different degree of complication in the drug development and also to some extent different costs in the clinical trials. By controlling for those disparities one gets a clear picture of the success of internal versus external projects. After controlling for project, company, and year characteristics, the probability of advancing a project from Phase II to Phase III is 20.7% lower for an alliance project than for an internally developed project. These results seem to indicate that having reached a more costly and complicated decision point, there was a reassessment of the real quality of the projects leading to the discontinuation of lower quality projects.

If one accepts that the decision to advance from Phase II to Phase III is a proxy of the quality of a project, then these results corroborate the prediction that the average quality of alliance projects is lower than the average quality of internal projects.

The ultimate definition of quality of a drug in the biopharmaceutical industry is whether a drug is approved by the FDA. In order to corroborate the above results, I run a regression of the probability of getting eventual FDA approval for a drug candidate that had a Phase III done. Table 8 presents the regression analysis. Indeed, not only do non-integrated projects advance with a lower probability to Phase III, but even those that do advance to Phase III have a lower probability of eventually getting FDA approval. Column 1 gives a simple comparison of means. An alliance project has a 9% lower chance of getting FDA approval than an internal project. This result holds using the standard controls; corroborating Prediction 2 that the average quality of an alliance project, as defined by it probability of success, is lower than the average quality of an internal project.

Even if one does not accept that the decision to advance from Phase II to Phase III is a proxy for quality, these results seem to indicate that the average quality of alliance projects is lower than the average quality of internal projects. When the firm decides at Phase II whether to advance to Phase III, it has more information than when it makes the decision to advance from Phase I to Phase II. Thus, one should expect this more informed decision to yield a better outcome, i.e. a higher probability of getting FDA approval. The fact that the probability of getting FDA approval for a non-integrated project is lower, indicates that indeed non-integrated projects are of lower quality.

5.1.3 Acquisitions

One potential criticism of the results in section 5.1 is that the controls do not account for something unique in the projects originated by the start-up companies. For this criticism to hold, one should expect that whatever makes those projects unique should still hold after the start-up is acquired by a larger firm.

Therefore, in order to corroborate the above results and in order to alleviate this potential criticism, I track start-up firms that had an alliance with a mature firm and subsequently were acquired by that mature firm[4]. I define an acquired project as a project that was originated (or its technology was originated) by a start-up company. The company was acquired and the clinical trials started *after* the company was acquired. Table 9 reports the result of the regression of the probability of a project advancing from Phase I to Phase II. All the projects in that sample are fully owned by the firm, but a subset of them was originated by companies that eventually were acquired by the firm. Column 1 is a comparison of means. The mean probability of a project moving from Phase I to Phase II is not statistically significantly different if the project was originated by a large firm or if it had been originated by a startup

[4]See Higgins and Rodriguez (2003) for an analysis of post alliance acquisitions.

but is now owned by the large firm. All these results hold with the regular sets of control used in section 5.1. This seems to indicate that what drives the above results is the organizational form governing the management of the project. Non-integrated projects seem to be treated differently by the firm, a situation that seems to change once the firm fully owns the project, making it fully integrated.

These results indicate that there seems to be something quite different in the decision mechanism, when a firm makes an resource allocation decision relating to integrated and non-integrated projects.

5.2 Allocation of Resources

Section 5.1 presents evidence that pharmaceutical firms are more prone to discontinue integrated projects than non-integrated projects when deciding whether to advance from Phase I to Phase II. It also presents evidence that those projects are of lower quality, both defined by the probability of advancing to Phase II and getting FDA approval. The model in Section 2 suggests that the reason that firms would promote further non-integrated projects that would yield lower quality projects is the rigidity of the contract governing them. Therefore, as Prediction 3 suggests, changes in the firm's financial condition should have a larger effect on internal projects than on external projects.

In order to test this prediction, I use several measures for factors that can affect the decision of a firm whether to continue an R&D project. First, I use the amount of cash (as measured by COMPUSTAT, in US Dollars deflated to the year 2000) the company has at the end of the year it started undertaking Phase I of the project. I normalize the amount of cash by the number of projects at that time in the firm. The results are very robust to different measures on normalization such as a weighted sum of projects, weighted by the expected cost of each project. Second, I use the number of other projects the firm has at the moment of decision. I normalize the number of projects by sales (in US Dollars deflated to the year 2000) of the firm that year so that they will proxy for the opportunity of the firm and not to its size. Again, the results using this variable are robust to using other deflators. All the regressions using the number of projects are robust to using only internal or internal and external projects. Third, I use not only the number of projects in the firm in general but also the number of projects in the firm targeting the same therapeutic class as the project I am looking at. This number is normalized in the same way as is the number of projects in the firm.

Table 10 presents the results of the regression of the probability of advancing from Phase I to Phase II on cash and the number of projects in the pipeline of the firm, using the same controls used in section 5.1. The proxy for the firm's financial constraint, the amount of cash the company has, affects the decision regarding internal projects but not external projects. The effect, though statistically significant, does not have a large economic significance. This is probably due to the fact that if they want, those large biopharmaceutical companies can raise added cash. These firms are sensitive in their decision to the cash at hand, indicating that they do not promote projects unless they have the resources to do so, and since they do not have endless resources they probably promote those projects that have the higher probability of success. When adding to the regression the overall number of projects in the firm we get a similar picture. The decision whether to advance from Phase I to Phase II is negatively related to the product pipeline. If the firm has many other projects (scaled by sales) it will be less likely to advance a specific project to the next phase. This result coupled with the cash result seems to indicate a behavior similar to "winner picking" by the firm. Projects are more likely to advance if there is more cash, less projects overall in the pipeline and if that specific project is more novel or targets a larger potential market. Non-integrated projects, on the other hand, don't seem to exhibit the same behavior. They don't seem to be very sensitive to either the amount of cash in the firm or the firm's pipeline. As prediction 3 suggests, this can be explained by the fact that non-integrated projects are governed by a pre set contract. If the projects meet their goals, it is very difficult to renegotiate (or break) the contract simply because the firm's opportunity set has changed. This rigidity seems to be at the heart of the above results. It must be noted that both integrated and non-integrated projects show sensitivity to the existence of a pipeline of projects in the same therapeutic class. This is not explicitly predicted by the model. This could be explained by the fact that if the firm has a similar project at the same stage it is easier for it to terminate an external project. This could be due to the fact that this public knowledge of such projects reduces the asymmetric information that is involved in the signal perceived by the termination of an alliance. In such a case, the market or other firms will know that the reason for termination of the contract is not bad results but a clear change in the firm's priority, mitigating any reputation problem that may arise generally from the discontinuation of an alliance.

Table 11 reports the results of a similar regression on the probability of advancing from Phase II to Phase III. The results are similar to Table 7 by showing that those projects that had advanced to Phase II among the alliance projects are of lesser quality. The sensitivities to cash and to the pipeline are very similar to Table 10.

6 Conclusion

In this paper I show that biopharmaceutical firms use different criteria in their allocation of resources when assessing integrated and non-integrated projects. The probability of a non-integrated project that is governed by a contract to advance from Phase I to Phase II is 20% higher. However, the probability of those projects to advance from Phase II to Phase III is 20% lower, and eventually they are 10% less likely to get FDA approval if they undertake Phase III. I interpret this result of having a lower probability of success as an indication of the project being of lower quality. These findings are robust to a set of project and company characteristics and controls. These results disappear once the non-integrated company is acquired by the larger firm.

It seems that the decision criteria employed by a firm when considering integrated and non-integrated projects are different. Integrated projects are sensitive to the amount of cash on hand and to the number of other unrelated projects in the firm. Non-integrated projects, however, are much less sensitive to cash and are not sensitive to the existence of other unrelated projects. All these results seem to indicate that biopharmaceutical firms make their resource allocation decisions regarding integrated projects in a manner reminiscent of “winner picking.” Given their financial constraint, they seem to pick the projects that have a higher probability of performing better. However, when dealings with non-integrated projects, it seems that the contract reduces the flexibility and latitude the firm has to terminate or even postpone a decision regarding the continuation of a project. This lack of flexibility results in promoting further non-integrated projects at the expense of better integrated projects. These projects eventually do not perform as well, resulting in a lower success rate.

There are a number of ways in which I hope to build on this research. First, this paper shows there is an inherent cost associated with an alliance compared to an acquisition. If so, it is not clear why most firms in this industry elect to conduct most of their dealing with start-up companies using a contract mechanism and not a simple acquisition. The cost of a purchase of a company is much higher since it involves essentially purchasing all the projects of that company. However, it is not clear what are the determinants of the decision to sign a contract on one project and not on the entire technology.

Second, Guedj and Scharfstein (2004) have shown that young companies are excessively prone to continue projects when they have the financial resources to do so. This paper shows that having such a project in an alliance with a larger firm does not resolve this over-investment problem. Since it seems difficult to discipline a start-up’s decision, there must be something valuable in those companies that entices either the market or more established companies to invest in them. Therefore, these start-ups have much lower success rates. Understanding the origin of the innovation of these companies and what makes them seem valuable (at least ex ante) and yet makes them not as successful is a very valuable question.

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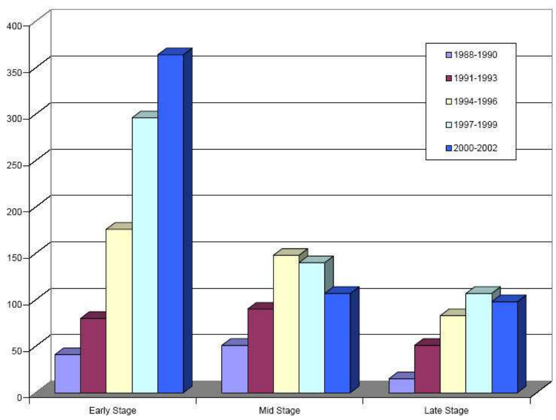

Figure 1: Number of alliances in the BioPharmaceutical industry in the years 1988-2002, grouped by the stage the alliance was signed at.

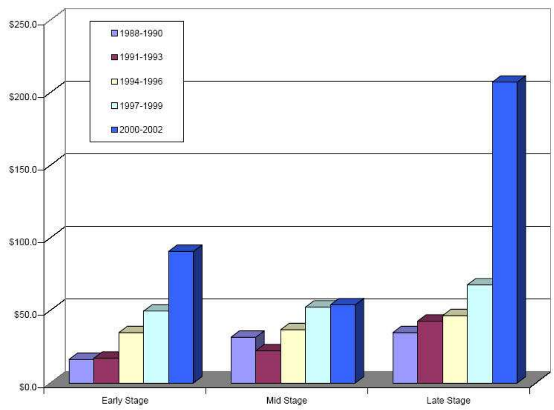

Figure 2: Average total size of an alliance (in US Dollars) in the BioPharmaceutical industry in the years 1988-2002, grouped by the stage the alliance was signed at.

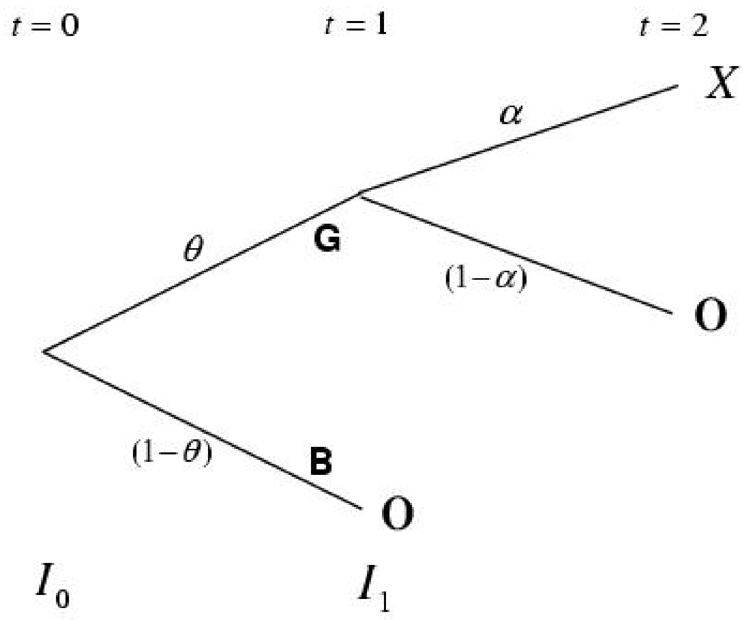

Figure 3: Timeline of the model.

Table 1: Time and Probability of Advancing from One Phase to Another

This table reports the time and probability of moving from one development phase to another. Panel A reports the number of drugs in the sample that moved from pre-clinical, to Phase I, Phase II, Phase III, and eventual FDA approval. Panel II reports the mean, median, and standard deviation of the time of moving from one phase to another. Time is measured in years.

Panel A: Success rate

	All		Internal		External	
	Number	Advance Rate	Number	Advance Rate	Number	Advance Rate
Number of Projects	4057		3610		447	
Went to Phase 1	2985	73.6 %	2567	71.1 %	418	93.5 %
Went to Phase 2	2108	70.6 %	1794	69.9 %	331	79.2 %
Went to Phase 3	1112	52.8 %	970	54.1 %	142	42.9 %
FDA Approval	671	60.3 %	597	61.5 %	74	52.1 %

Panel B: Time to Next Stage (in years)

		All	Internal	External
Time to Phase 1	Mean	0.70	0.68	0.82
Time to Phase 1	Median	1.10	1.10	1.08
Time to Phase 1	Std	0.53	0.53	0.48
Time to Phase 2	Mean	1.69	1.70	1.47
Time to Phase 2	Median	1.82	1.90	1.50
Time to Phase 2	Std	1.17	1.14	1.39
Time to Phase 3	Mean	2.40	2.38	2.51
Time to Phase 3	Median	2.60	2.60	2.60
Time to Phase 3	Std	1.10	1.10	1.16
Time to Approval	Mean	2.91	2.88	3.10
Time to Approval	Median	2.74	2.74	2.74
Time to Approval	Std	1.02	1.00	1.13
Time to cancellation	Mean	2.85	2.78	3.75
Time to cancellation	Median	2.17	2.09	3.59
Time to cancellation	Std	2.38	2.38	2.17
Clinical Time to Approval	Mean	8.07	8.09	7.92
Clinical Time to Approval	Median	8.88	8.88	8.95
Clinical Time to Approval	Std	1.84	1.85	1.79

Table 2: Therapeutic Classes

This table reports the breakdown of projects by therapeutic classes. The therapeutic activity codes, as defined in the Pharmaprojects Therapeutic Classification System (PTCS). This classification is based on the original classification devised by the European Pharmaceutical Market Research Association (EPhMRA). The PTCS differs from the EPhMRA classification in that it has been considerably revised to more accurately reflect the types of products in R&D in 2004, rather than the marketed products of the 1970s. The PTCS is divided into fourteen major sections covering broad therapeutic areas, such as blood and clotting products, anticancer agents or respiratory agents. This classification is similar to the World Health Organization's (WHO) typology used by Danzon, Nicholson, and Pereira (2003).

Therapeutic Class	Total	Internal	External
Alimentary/Metabolic	348	286	62
Anti-infective	749	654	95
Anticancer	442	396	46
Antiparasitic	18	18	0
Blood/clotting	203	197	6
Cardiovascular	653	631	22
Dermatological	78	67	11
Genitourinary and Sex Hormones	112	99	13
Hormones excluding Sex Hormones	65	63	2
Immunological	71	56	15
Musculoskeletal	272	244	28
Neurological	735	636	99
Respiratory	292	250	42
Sensory	19	13	6
Total	4057	3610	447

Table 3: Control Variables

This table reports summary statistics on two control variables used in this study.
Panel A reports the distribution of the potential market size of the drug projects in this study, This distribution is based on assessments made by *PharmaProjects*.
Panel B reports data on the "novelty" of the drugs developed. Novelty is defined using the pharmacological description of the drugs. The pharmacology describes a drug's mechanism of action in the body, through which it exerts its therapeutic effect, i.e. it identifies the biological agent or process the drug stimulates or inhibits. Panel B describes the mean "rank" of each drug. Each drug is ranked in chronological order of appearance of its pharmacological mechanism for its specific therapeutic class of in the sample of all the compounds developed in the past 20 years as reported by *PharmaProjects*.

Panel A: Distribution of Estimated Project Potential Market Size

Market Size	Internal	Alliance
US$ 0-500 million	9.2 %	7.9 %
US$ 501-2000 million	29.8 %	33.8 %
US$ 2001-5000 million	35.5 %	37.1 %
US$ 5001-10000 million	16.1 %	9.1 %
Over US$ 10000 million	8.1 %	9.4 %

Panel B: Mean Rank of drug Novelty

	Mean	Median	Std
Internal Projects	24.07	8	48.07
Alliance Projects	28.31	10	50.11

Table 4: Summary Statistics on Sample Companies

This table reports summary statistics on the firms in the sample. The numbers are averages of all the firm-year observations. Sales, assets, cash, market cap are in Millions of Dollars. Number of employees is in thousands. Q is defined as the market value of equity the book value of assets less the book value of equity divided by the book value of assets. All the numbers are deflated to year 2000 Dollars.

Statistic	Sales	Assets	Cash	R&D	Market Cap	Q	Employees
Mean	9,751.33	12,663.86	2,158.25	1,034.74	32,684.01	3.45	38.84
Median	8,030.59	10,952.53	1,314.33	934.27	27,952.96	3.51	42.22
Std	9,691.63	12,219.54	3,053.65	844.02	28,937.93	1.09	35.76
Max	35,198.89	42,362.05	12,629.75	2,945.42	106,737.00	6.71	136.61
Min	14.08	277.71	179.91	40.70	606.57	1.52	0.17
25%	1,029.82	2,318.71	485.73	279.91	5,918.06	2.74	4.25
75%	15,350.96	18,720.97	2,489.55	1,716.58	55,619.64	4.03	52.16

Table 5: Regression of the Probability of Advancing from Phase I to Phase II

The model estimated is a linear probability regression. The dependent variable is the probability of advancing from phase I to phase II in the 2 years following phase I. It takes the value of 1 if the drug advanced to phase II and 0 if not. An alliance project is defined as a project that was originated by another company and an alliance contract was signed. There are several controls: 1) Novelty - Each compound has a pharmacological description (a drug's mechanism of action in the body, through which it exerts its therapeutic effect). Compounds are ranked by the number of drugs developed for the same therapeutic class with the same pharmacological description over time. Novelty is the log of the inverse of this rank. 2) Bio - a dummy that receives a value of 1 if the compound is based on a biologic agent and 0 if not. 3) Market Size - There are three dummies as defined by *The PharmaProjects*: market size is up to 2000$m, between 2000 and 5000$m and more than 5000$m. 4) Three fixed effects: company fixed effects, therapeutic class fixed effects and year fixed effects. The t-statistics, reported in parentheses, are based on robust standard errors that are corrected for firm-level clustering.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Alliance	0.1591	0.1621	0.1763	0.197	0.1951	0.1969	0.2074
	(7.71)***	(5.69)***	(5.43)***	(5.02)***	(5.19)***	(5.12)***	(4.68)***
Novelty		0.0255	0.0256	0.0272	0.0304	0.0297	0.0289
		(2.24)**	(2.28)**	(2.45)**	(2.61)**	(2.51)**	(2.55)**
Bio			0.0778	0.0817	0.0700	0.0735	0.0772
			(2.46)**	(2.51)**	(2.32)**	(2.34)**	(2.37)**
Market Size - Large				0.0397	0.0666	0.0582	0.1535
				(0.30)	(0.50)	(2.33)**	(2.42)**
Market Size - Small				-0.0532	-0.045	-0.0426	-0.0279
				(2.20)**	(1.96)*	(1.72)*	(1.32)
Observations	2985	2985	2985	2985	2985	2985	2985
R^2	0.10	0.11	0.11	0.11	0.14	0.15	0.25
Company FE	No	No	No	No	Yes	Yes	Yes
Therapeutic Class FE	No	No	No	No	No	Yes	Yes
Year FE	No	No	No	No	No	No	Yes

Table 6: Regression of the Probability of Advancing from Phase I to Phase II - 3 Year Cutoff

The model estimated is a linear probability regression. This model is identical to table 5 expect for a variation on the dependent variable. The dependent variable is the probability of advancing from phase I to phase II in the **3** years following phase I. It takes the value of 1 if the drug advanced to phase II and 0 if not. An alliance project is defined as a project that was originated by another company and an alliance contract was signed. There are several controls: 1) Novelty - Each compound has a pharmacological description (a drug's mechanism of action in the body, through which it exerts its therapeutic effect). Compounds are ranked by the number of drugs developed for the same therapeutic class with the same pharmacological description over time. Novelty is the log of the inverse of this rank. 2) Bio - a dummy that receives a value of 1 if the compound is based on a biologic agent and 0 if not. 3) Market Size - There are three dummies as defined by *The PharmaProjects*: market size is up to 2000$m, between 2000 and 5000$m and more than 5000$m. 4) Three fixed effects: company fixed effects, therapeutic class fixed effects and year fixed effects. The t-statistics, reported in parentheses, are based on robust standard errors that are corrected for firm-level clustering.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Alliance	0.1399	0.1518	0.1622	0.1713	0.1856	0.1911	0.2007
	(6.01)***	(5.60)***	(5.52)***	(4.96)***	(5.01)***	(4.92)***	(4.42)***
Novelty		0.0256	0.0261	0.0256	0.023	0.021	0.0199
		(2.40)**	(2.30)**	(2.25)**	(2.22)**	(2.02)**	(1.97)*
Bio			0.0298	0.031	0.0301	0.0295	0.0313
			(2.30)**	(2.36)**	(2.28)**	(2.30)**	(2.32)**
Market Size - Large				0.0233	0.0152	0.017	0.0465
				(1.20)	(1.12)	(2.30)**	(2.51)**
Market Size - Small				-0.0176	-0.0167	-0.0028	-0.0153
				(0.96)	(0.96)	(0.14)	(0.94)
Observations	2892	2892	2892	2892	2892	2892	2892
R^2	0.09	0.14	0.14	0.14	0.15	0.16	0.23
Company FE	No	No	No	No	Yes	Yes	Yes
Therapeutic Class FE	No	No	No	No	No	Yes	Yes
Year FE	No	No	No	No	No	No	Yes

Table 7: Regression of the Probability of Advancing from Phase II to Phase III

The model estimated is a linear probability regression. The dependent variable is the probability of advancing from phase II to phase III in the 3 years following phase I. It takes the value of 1 if the drug advanced to phase II and 0 if not. An alliance project is defined as a project that was originated by another company and an alliance contract was signed. There are several controls: 1) Novelty - Each compound has a pharmacological description (a drug's mechanism of action in the body, through which it exerts its therapeutic effect). Compounds are ranked by the number of drugs developed for the same therapeutic class with the same pharmacological description over time. Novelty is the log of the inverse of this rank. 2) Bio - a dummy that receives a value of 1 if the compound is based on a biologic agent and 0 if not. 3) Market Size - There are three dummies as defined by *The PharmaProjects*: market size is up to 2000$m, between 2000 and 5000$m and more than 5000$m. 4) Three fixed effects: company fixed effects, therapeutic class fixed effects and year fixed effects. The t-statistics, reported in parentheses, are based on robust standard errors that are corrected for firm-level clustering.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Alliance	-0.0894	-0.1021	-0.0956	-0.1048	-0.1276	-0.1462	-0.1742
	(2.49)**	(2.52)**	(2.96)***	(3.47)***	(3.45)***	(3.54)***	(3.90)***
Novelty		0.0563	0.0744	0.0545	0.1001	0.1313	0.1520
		(2.29)**	(2.37)**	(2.42)**	(2.52)**	(2.96)***	(2.60)**
Bio			-0.0571	-0.0457	-0.0605	-0.0617	-0.0562
			(1.21)	(1.12)	(1.08)	(1.10)	(1.05)
Market Size - Large				0.0239	0.0325	0.0386	0.0297
				(1.25)	(1.27)	(1.32)	(1.28)
Market Size - Small				-0.0282	-0.0179	-0.0025	-0.0095
				(0.90)	(0.84)	(0.10)	(0.50)
Observations	2108	2108	2108	2108	2108	2108	2108
R^2	0.08	0.08	0.09	0.09	0.13	0.23	0.28
Company FE	No	No	No	No	Yes	Yes	Yes
Therapeutic Class FE	No	No	No	No	No	Yes	Yes
Year FE	No	No	No	No	No	No	Yes

Table 8: Regression of the Probability of Getting FDA Approval if Moved to Phase III

The model estimated is a linear probability regression. The dependent variable is the probability of receiving FDA approval in the 4 years following Phase III. It takes the value of 1 if the drug received FDA approval and 0 if not. An alliance project is defined as a project that was originated by another company and an alliance contract was signed. There are several controls: 1) Novelty - Each compound has a pharmacological description (a drug's mechanism of action in the body, through which it exerts its therapeutic effect). Compounds are ranked by the number of drugs developed for the same therapeutic class with the same pharmacological description over time. Novelty is the log of the inverse of this rank. 2) Bio - a dummy that receives a value of 1 if the compound is based on a biologic agent and 0 if not. 3) Market Size - There are three dummies as defined by *The PharmaProjects*: market size is up to 2000$m, between 2000 and 5000$m and more than 5000$m. 4) Three fixed effects: company fixed effects, therapeutic class fixed effects and year fixed effects. The t-statistics, reported in parentheses, are based on robust standard errors that are corrected for firm-level clustering.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Alliance	-0.0929	-0.0961	-0.0913	-0.0953	-0.105	-0.1133	-0.1089
	(2.09)**	(2.06)**	(2.18)**	(2.21)**	(2.54)**	(2.34)**	(3.10)***
Novelty		-0.0753	-0.0779	-0.0716	-0.0787	0.0364	-0.1016
		(0.63)	(0.31)	(0.57)	(0.61)	(0.27)	(1.16)
Bio			-0.1179	-0.1238	-0.1061	-0.1114	-0.1170
			(1.76)*	(1.79)*	(1.61)	(1.30)	(1.19)
Market Size - Large				0.0479	0.0759	0.1715	0.0476
				(1.95)*	(1.27)	(1.35)	(1.21)
Market Size - Small				0.017	0.0181	0.0138	0.0244
				(0.55)	(0.58)	(0.40)	(0.79)
Observations	997	997	997	997	997	997	997
R^2	0.08	0.10	0.11	0.11	0.13	0.15	0.16
Company FE	No	No	No	No	Yes	Yes	Yes
Therapeutic Class FE	No	No	No	No	No	Yes	Yes
Year FE	No	No	No	No	No	No	Yes

Table 9: Regression of the Probability of Advancing from Phase I to Phase II - Acquisitions

The model estimated is a linear probability regression. The dependent variable is the probability of advancing from phase I to phase II in the 2 years following phase I. It takes the value of 1 if the drug advanced to phase II and 0 if not. n acquired project is a project that belonged to a smaller firm (that had in the past a contractual alliance with the larger firm) but subsequently got acquired by the larger firm. There are several controls: 1) Novelty - Each compound has a pharmacological description (a drug's mechanism of action in the body, through which it exerts its therapeutic effect). Compounds are ranked by the number of drugs developed for the same therapeutic class with the same pharmacological description over time. Novelty is the log of the inverse of this rank. 2) Bio - a dummy that receives a value of 1 if the compound is based on a biologic agent and 0 if not. 3) Market Size - There are three dummies as defined by *The PharmaProjects*: market size is up to 2000$m, between 2000 and 5000$m and more than 5000$m. 4) Three fixed effects: company fixed effects, therapeutic class fixed effects and year fixed effects. The t-statistics, reported in parentheses, are based on robust standard errors that are corrected for firm-level clustering.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Alliance Acquisition	-0.0104	-0.0085	-0.0099	-0.0098	-0.0119	-0.0147	-0.0202
	(0.49)	(0.39)	(0.45)	(0.45)	(0.48)	(0.60)	(0.96)
Novelty		0.0403	0.0401	0.0425	0.0468	0.0454	0.0322
		(3.40)***	(3.43)***	(3.75)***	(3.95)***	(3.80)***	(3.61)***
Bio			0.0738	0.0775	0.0664	0.0697	0.0732
			(2.41)**	(2.56)**	(2.42)**	(2.30)**	(2.25)**
Market Size - Large				0.4150	0.05987	0.06875	0.0824
				(0.50)	(0.72)	(1.33)	(1.74)*
Market Size - Small				-0.0732	-0.0677	-0.068	-0.0468
				(2.75)***	(2.66)**	(2.43)**	(2.16)**
Observations	2567	2567	2567	2567	2567	2567	2567
R^2	0.00	0.01	0.02	0.02	0.05	0.07	0.12
Company FE	No	No	No	No	Yes	Yes	Yes
Therapeutic Class FE	No	No	No	No	No	Yes	Yes
Year FE	No	No	No	No	No	No	Yes

Table 10: Regression of the Probability of Advancing from Phase I to Phase II - Resource Allocation Across Different Projects

The model estimated is a linear probability regression. The dependent variable is the probability of advancing from phase I to phase II in the 2 years following phase I. It takes the value of 1 if the drug advanced to phase II and 0 if not. An alliance project is defined as a project that was originated by another company and an alliance contract was signed. 1) Cash is the amount of cash (deflated to year 2000 Dollar terms) the company has scaled by the total number of projects the company had 3 years earlier. 2) All Projects - is the total number of projects in the firm scaled by the firm's sales (deflated to year 2000 Dollar terms). 3) Same Therapy Projects - is the total number of projects in the firm targeting the same therapeutic class scaled by the firm's sales (deflated to year 2000 Dollar terms). The same controls are used as described in Table 5. The t-statistics, reported in parentheses, are based on robust standard errors that are corrected for firm-level clustering.

	(1)	(2)	(3)	(4)	(5)
Alliance	0.0860	0.1081	0.1191	0.1635	0.1771
	(2.61)**	(2.32)**	(2.71)**	(3.18)***	(3.10)***
Cash	0.0012	0.0019	0.0019	0.0013	0.0023
	(8.02)***	(6.24)***	(6.21)***	(4.45)***	(6.08)***
Cash*Alliance	0.0000	0.0001	0.0001	0.0001	0.0004
	(0.22)	(1.00)	(1.00)	(1.00)	(1.00)
All Projects		-0.0039	-0.0030	-0.0070	-0.0089
		(1.95)**	(1.98)**	(2.92)***	(2.96)***
All Projects*Alliance		0.0028	0.0034	0.0018	0.0006
		(1.64)	(1.95)**	(0.91)	(0.19)
Same Therapy		-0.0192	-0.0190	0.0137	-0.0134
Projects		(1.84)*	(1.80)*	(2.01)**	(2.05)**
Same Therapy		-0.0146	-0.0166	-0.0174	-0.0145
Projects*Alliance		(1.99)**	(1.97)**	(2.52)***	(2.85)***
Novelty	0.0132	0.0121	0.0110	0.0106	0.0376
	(1.90)*	(1.97)**	(2.12)**	(2.23)**	(2.65)**
Bio	0.0635	0.0743	0.0760	0.0734	0.0980
	(1.95)*	(2.17)**	(2.32)**	(2.41)**	(2.60)**
Market Size - Large	0.0669	0.0139	0.0036	0.0954**	0.1250**
	(1.01)	(0.17)	(0.04)	(2.11)	(2.03)
Market Size - Small	0.0275	0.0360	0.0316	0.0361	0.0241
	(0.76)	(1.39)	(1.15)	(1.26)	(0.81)
Observations	2985	2985	2985	2985	2985
R^2	0.13	0.14	0.15	0.16	0.27
Company FE	No	No	Yes	Yes	Yes
Therapeutic Class FE	No	No	No	Yes	Yes
Year FE	No	No	No	No	Yes

Table 11: Regression of the Probability of Advancing from Phase II to Phase III - Resource Allocation Across Different Projects

The model estimated is a linear probability regression. The dependent variable is the probability of advancing from phase II to phase III in the 3 years following phase II. It takes the value of 1 if the drug advanced to phase III and 0 if not. An alliance project is defined as a project that was originated by another company and an alliance contract was signed. 1) Cash is the amount of cash (deflated to year 2000 Dollar terms) the company has scaled by the total number of projects the company had 3 years earlier. 2) All Projects - is the total number of projects in the firm scaled by the firm's sales (deflated to year 2000 Dollar terms). 3) Same Therapy Projects - is the total number of projects in the firm targeting the same therapeutic class scaled by the firm's sales (deflated to year 2000 Dollar terms). The same controls are used as described in Table 5. The t-statistics, reported in parentheses, are based on robust standard errors that are corrected for firm-level clustering.

	(1)	(2)	(3)	(4)	(5)
Alliance	-0.1286	-0.1222	-0.1157	-0.1358	-0.1513
	(1.72)*	(1.74)*	(2.81)***	(2.69)***	(2.74)***
Cash	-0.0002	0.0001	-0.0002	-0.0002	-0.0004
	(4.95)***	(0.28)	(6.01)***	(2.26)**	(2.72)***
Cash*Alliance	0.0001	0.0001	0.0000	-0.0001	0.0000
	(0.31)	(0.28)	(0.19)	(0.60)	(0.07)
All Projects		-2.8213	-2.0406	-2.9431	-3.0120
		(1.36)	(1.25)	(2.01)**	(2.36)**
All Projects*Alliance		-0.3087	-0.6497	-0.4893	-0.1409
		(0.68)	(0.36)	(0.68)	(0.48)
Same Therapy Projects		-1.5149	-1.2709	-1.2167	-1.1625
		(2.27)**	(2.18)**	(2.12)**	(2.31)**
Same Therapy Projects*Alliance		-1.7123	-1.6750	-1.5430	-1.3056
		(4.64)***	(3.98)***	(2.88)***	(2.27)**
Novelty	0.0132	0.0121	0.0110	0.0106	0.0376
	(1.90)*	(1.97)**	(2.12)**	(2.23)**	(2.65)**
Bio	-0.0635	-0.0743	-0.0760	-0.0734	-0.0780
	(1.95)*	(1.25)	(1.32)	(1.41)	(1.60)
Market Size - Large	-0.0262	0.1252	0.1155	0.0879*	0.0809*
	(0.24)	(0.93)	(0.89)	(1.94)	(1.89)
Market Size - Small	0.0893	0.0057	0.0097	-0.0126	-0.0157
	(2.70)***	(0.17)	(0.28)	(0.45)	(0.54)
Observations	2108	2108	2108	2108	2108
R^2	0.10	0.11	0.14	0.24	0.28
Company FE	No	No	Yes	Yes	Yes
Therapeutic Class FE	No	No	No	Yes	Yes
Year FE	No	No	No	No	Yes