A Breath of Fresh Air? Firm types, scale, scope and selection effects in drug development

Arora, Ashish and Gambardella, Alfonso and Magazzini, Laura and Pammolli, Fabio

IMT Institute For Advanced Studies, Lucca

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A Breath of Fresh Air?
Firm type, scale, scope and selection effects in drug development

Ashish Arora
Heinz School, Carnegie Mellon University, Pittsburgh, PA, & Fuqua School of Business, Duke University
ashish@andrew.cmu.edu

Alfonso Gambardella
Bocconi University, Milan, Italy
alfonso.gambardella@unibocconi.it

Laura Magazzini
Dept. of Economics, University of Verona, Italy
laura.magazzini@univr.it

Fabio Pammolli
University of Florence, and IMT – Lucca Institute for Advanced Studies, Italy
pammolli@gmail.com

This paper compares the innovation performance of established pharmaceutical firms with biotech companies, controlling for differences in the scale and scope of research. We develop a structural model estimated with data on over 3,000 drug R&D projects in preclinical and clinical trials in the US from 1980-94, and followed till 2005. Key to our approach is careful attention to the issue of selection. Firms choose which compounds to advance into clinical trials. This choice depends not only on the technical promise of the compound, but also on commercial considerations such as the expected profitability of the market or concerns about product cannibalization. After controlling for selection, we find that: a) even after controlling for scale and scope in research, established pharmaceutical firms have superior innovation performance than newly entered biotech firms; b) older biotech firms are more similar to the established firms both in terms of selection behavior and innovation performance; c) compounds licensed by pharmaceutical firms are as likely to succeed as internal developed projects of the licensor, which is inconsistent with the “lemons” hypothesis in technology markets.

Key words: firm capabilities, drug development process, market for technology.
1. Introduction

Understanding the determinants of the innovative performance of firms is central to innovation and entrepreneurship research. Yet, the development of innovations by firms is not just a matter of technical ability. Incentives matter as well. A classical example is Arrow (1962), whereby larger firms have lower incentives to innovate, for fear of cannibalizing existing products. Similarly, if a firm faces a larger potential market or has established downstream commercialization capabilities, it will have higher innovation incentives. Therefore, in studying the drivers of innovation performance, it is important to distinguish between incentives and capability, as one may confound lack of incentives with lower technical capabilities or vice versa.

A key contribution of this paper is to develop and estimate a structural model that distinguishes between these two dimensions. We use data on more than 3,000 drug R&D projects initiated between 1980 and 1994, and followed till 2005. The pharmaceutical industry is ideal for our analysis because the drug innovation process follows well defined steps. New compounds are generated in the laboratory (initial discovery), tested on animals (pre-clinical research), and if the firm considers them sufficiently promising, both technically and economically, they are advanced into clinical trials on humans. This process has two important regulatory gates: At the beginning of clinical trials, when an IND (Investigational New Drug) application is filed, and at the end of the clinical trials, when an NDA (New Drug Application) may be filed. These two main stages play an important role in our analysis.

We argue that firms do not move all technically promising compounds to clinical trials; instead, economic considerations are also important in making this decision, creating differences in selection behavior across firms. Thus, if one measured innovation capability by the share of pre-clinical compounds that eventually become new drugs, one may confound selection with capability (e.g., Shaver, 1998).

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1 See e.g. [http://www.fda.gov/cder/handbook/](http://www.fda.gov/cder/handbook/). See also FDA (1999) or DiMasi et al. (2003).
The contribution of this paper to the literature goes beyond the mere flagging of the selection problem and the development of a method for coping with it. We focus on two questions that can be studied particularly well in the context of the pharmaceutical industry.

The first one is the long-standing comparison between the innovation performance of large and small firms (e.g., Arrow 1983; Holmstrom 1989; Acs and Audretsch 1990; Henderson and Clark 1990; Chesbrough and Teece 1996; Levinthal and March 1993). One view holds that small firms have more flexible organizations that enhance creativity and attract more inventive minds, which makes them more productive in R&D, whereas large firms have an advantage in commercialization. A different view holds that economies of scale and scope, and learning advantages, make the larger firms better at innovation (e.g., Henderson and Cockburn 1996, Macher and Boerner 2006). The comparative advantage of small firms may lie in exploring technologies and markets that established firms are unwilling to explore (Christensen 1997; Klepper and Thompson, 2006; Giarratana 2004). We cannot directly measure comparative advantage. However, because R&D in the drug industry is performed by both large, established firms and smaller biotech firms, we can estimate whether these types differ in their ability to develop compounds successfully, which is our measure of innovation performance.

Our second question is whether “markets for technology” (Arora et al., 2001) are afflicted by a “lemons” problem (Akerlof, 1970): Are compounds offered for license of lower quality than compounds developed in-house? The current evidence is mixed. Danzon et al. (2005) find a positive effect of licensing on the probability of success of drug compounds, while Pisano (1997) and Guedj (2005) find that licensed drugs are less successful than those developed in-house. Our paper offers a test of these two contending views.

The next section reviews the main findings of the empirical literature on drug development in the pharmaceutical industry, and it places our contribution in context. Section 3 describes the model and Section 4 develops our hypotheses. Section 5 describes our data and analysis. Section 6 discusses our estimates. Section 7 discusses the robustness of our results and concludes.
2. Innovation in Pharmaceuticals: The Related Literature

One group of studies on drug innovation focuses on the internal economies of the firm (economies of scale, scope, spillovers, experience). Henderson and Cockburn (1996) study the determinants of research (drug discovery) performance, measured by the number of important drug patents. They use data at the level of the individual research program from the internal records of ten major pharmaceutical firms, and find returns to scale at the level of both individual research programs and the research expenditures of the firm as a whole, as well as evidence of economies of scope. Our paper investigates the stages after drug discovery, as do most of the other studies described below.

Nerkar and Roberts (2004) examine the determinants of commercial success of new pharmaceutical products. They find that proximal technological experience (patents in the same therapeutic class) has a positive and significant effect on the first-year sales of a new product. Distal technological experience is positive and significant only when accompanied by a high level of distal product-market experience. Finally, they find that the interaction between distal and proximal technological experience is negative, which suggests that focused and diversified innovations may be alternative strategies. Nerkar (2003) also studies the relationship between experience and the probability that a drug receives FDA approval. He hypothesizes that experience may not always lead to better performance, if the experience is of the wrong sort (e.g., oriented towards drug discovery rather than drug development), and if feedback is inadequate or delayed. With drug development cycles stretching to ten years or more, researchers may be rewarded for discovery (measured by patenting) rather than commercialization (measured by FDA approval). As a result, scientists may continue to work in areas that provide them with clumps of patents but do not lead to commercially useful drugs. As we discuss below, even small firms may suffer from a misalignment of incentives, as reflected in their selection behavior.

A second group of studies looks specifically into the drug development process by using data for projects in clinical trials. Adams and Brantner (2003) and Abrantes-Metz et al. (2006) analyze drugs in clinical trials around the world between 1989 and 2002. They find that success rates and durations can
vary substantially across observable characteristics of the drugs, including primary indication, originating company, route of administration and chemistry. Macher and Boerner (2006) also estimate time to complete clinical trials, but by contract research organizations (CRO) rather than integrated R&D projects in pharmaceutical firms. They find that scale and scope economies, and experience are valuable.

Danzon et al. (2005) focus on the role that experience (both overall experience and experience in a particular therapeutic category) and alliances have on the outcome of R&D projects. Their sample is composed of R&D projects of over 900 firms during 1988-2000. They too find evidence of large positive returns to a firm’s overall experience for the larger and more complex late-stage trials. They recognize, but do not explicitly model, differences across firms in the quality of their drug candidates.

Our paper shares the approach and the goals of all these papers. However, none of these papers addresses explicitly the concern that firms may systematically vary in how selective they are in advancing compounds into clinical trials. As is well known, clinical trials are much more expensive than pre-clinical trials, particularly late stage clinical trials. Which compounds make it into clinical trials depends upon whether managers think the compounds are promising. All else equal, a compound with a higher likelihood of successfully gaining FDA approval is more likely to get selected into clinical trials than a compound with a lower probability of success.

But commercial considerations are also very important. Acemoglu and Linn (2004) present evidence that larger pharmaceutical markets see more innovation. Further, a firm with downstream marketing capabilities in a particular market (such as BMS in anti-cancer or Merck in cardiovascular) may be able to extract greater value from a drug than a firm that lacks such capabilities, and therefore be willing to take a chance on a compound with a lower likelihood of success. Other considerations may also be important. A drug championed by a high status research team may be selected for clinical trials, even if it is below threshold (Nerkar 2003). Guedj and Scharfstein (2005) point to the agency problem between managers and investors. In biotech startups, managers typically have one or two compounds to bet upon, and therefore try to push them into clinical trials. By contrast, larger firms have many compounds from which to choose, and are less likely to have a vested interest in any particular
compound. As a result, biotech companies are more likely to advance products from phase I into phase II clinical trials, but these compounds are more likely to fail in later stages (Guedj and Scharfstein, 2005). In our paper, we distinguish between the pre-clinical and clinical trials, but do not separately analyze the progress across the various clinical stages.

To appreciate further the contribution of our paper, it may be useful to compare it with Chandy et al. (2006), who examine the “conversion ability” of firms in translating drug-related patents into new drugs. They find that conversion ability is greatest in firms that develop an intermediate number of drug-related patents. Since firms patent compounds soon after discovery, Chandy et al (2006), in essence, study the success rate of pre-clinical compounds. Our analysis “unpacks” this sequence into whether the compound is selected into clinical trials, and if selected, whether it successfully receives FDA approval, and models the drivers of the underlying processes. This enables us to move away from the assumption implicit in Chandy et al. that firms attempt to convert every compound. Instead, our model allows the stringency of selection to be driven by the expected profitability of the market, the scale and scope of the firm, and other technology, market, and firm characteristics, so that the rate at which pre-clinical compounds succeed is determined by the factors that drive innovation performance, but also by factors that drive selection into clinical trials. In econometric terms, what allows us to identify selection is that the major resource commitments are made in clinical trials rather than pre-clinical trials (DiMasi, et al. 2003), so that we can assume that commercial considerations affect selection, but not the outcomes once the compound is into clinical trials.

Finally, the literature addresses the question of whether licensed compounds are more likely to succeed compared to integrated projects. The market for technology perspective (Arora et al. 2001) suggests that smaller technology specialist firms and established manufacturers have comparative advantages in different stages of the innovation process. In particular, technology specialists are relatively more effective in upstream innovation activities that rely on creativity rather than downstream development and commercialization, which is intensive in resources and scale. Licensing permits the technology specialists to “cooperate” with established incumbents downstream, increasing overall
efficiency. Similarly, the network literature (e.g., Powell et al. 1996; Pammolli and Riccaboni 2004) posits that resources are located in networks rather than individual firms. Thus, licensed compounds, which exploit resources available in different organizations, can better exploit the fit between resource types and the specific innovation tasks. This view, however, is agnostic that licensed compounds are more likely to succeed than other compounds. Rather, licensing is an efficient use of resources, increasing not necessarily the overall success rate, but rather lowering the cost of successfully developing a drug.

Zeckhauser (1996), and Pisano (1997 and 2006) argue that technology markets inefficient, and are potentially afflicted by a “lemons” problem. Pisano (1997) finds that in-house development is superior to licensed compounds, and Guedj (2005) finds that projects financed by pharmaceutical companies but developed by biotech firms are more likely to fail. On the other hand, Danzon et al. (2005) find that compounds developed in alliances (roughly equivalent to licensed compounds) have a lower probability of failure in clinical trials. However, Danzon et al. (2005) include in their sample alliances that were formed prior to the conclusion of each phase (up to phase III). These alliances are likely to include marketing agreements that pharmaceutical firms often strike for successful compounds to enhance market access, implying an upward biased estimate. We follow Guedj (2005) and only include licenses signed before phase I clinicals, and test whether licensed compounds differ from in-house compounds.

However, comparing compounds discovered by biotech firms and licensed to pharmaceutical firms to those discovered in-house by pharmaceutical firms is not the correct way to test for a lemons problem. A lemons problem would exist if biotech firms systematically licensed inferior drugs to pharmaceuticals and kept superior ones in-house. Thus, we estimate whether licensed compounds are drawn from a different distribution than those that biotech firms develop in-house.

3. An Econometric Model of Selection and Success

To understand the interplay between selection and success we provide a simple model. After the compound has been discovered, the firm starts preclinical trials to evaluate its properties. Preclinical research will provide the firm with an estimate of the probability that the compound will succeed i.e., pass
the clinical trials and receive FDA approval. Let Pg be the firm’s (unbiased) point estimate of the
(uncertain) probability of success of a particular compound. We will sometimes refer to this as the quality
of the compound. Formally, $P_{g_{ij}}$, the probability that compound $i$ of firm $j$ will pass clinical trials, is a
random variable drawn from a distribution with a firm specific mean, $\mu_j$ (the innovative capability of the
firm). Actual success or failure is only observed for compounds selected for clinical trials.

**Selection:** Dropping the subscripts for compound and firm to avoid clutter, let $V$ indicate the expected net
additional revenue from the sales of the compound if it is eventually marketed, and $D$ the net additional
clinical trial costs, which we label development costs. The firm will take the compound into clinical trials
if it expects a net profit from its development i.e. if $PgV - D > 0$, or $Pg > D/V$. We denote $D/V$ as $Pg^*$, a
threshold that is a function of $V$ and $D$. Note that $Pg^*$ is not a random variable but a threshold value. The
probability of a compound being selected depends both on the threshold, $Pg^*$, and the “quality” of the
compound, $Pg$, where the latter is itself a random variable. Thus the average probability that a compound
is selected depends upon $Pg^*$ and $\mu$.

The selection threshold, $Pg^*$, represents the economic and strategic dimension of selection. For
instance, firms with full pipelines of drugs under development will assess a higher net addition to
development costs ($D$) and hence have a high $Pg^*$. Market profitability matters as well. To anticipate our
empirical analysis, competition in the product market will reduce the expected value, $V$ implying a higher
$Pg^*$. Similarly, larger markets will increase $V$, implying a lower $Pg^*$. Also, public firms may have a
lower cost of capital, implying a lower $D$, and hence, a lower $Pg^*$.

We assume that once a compound enters clinical trials, its future progress in clinical trials is
determined only by its technical characteristics. Our interviews with industry executives suggest that over
the course of development, the relative importance of the technical characteristics increases. Early in
drug development, commercial considerations such as the size of the market, the extent of competition in
the market, and the firm’s relevant commercialization capabilities, condition the selection threshold. As

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2 In the empirical analysis, $\mu$ will also differ by therapeutic area.
the compound progresses, more and more information about its safety and efficacy becomes available, so that outcomes become more deeply imbued by the technical (therapeutic) characteristics of the compound, namely, how effective the compound is against a particular condition and its long term side-effects. We simplify by assuming that both technical promise, $P_g$, and commercial considerations, represented by $P_g^*$, determine selection. However, once selected, the FDA approval takes place with probability $P_g$. Since we do not observe $P_g$, the expected probability of FDA approval is the expected value of $P_g$, conditional upon $P_g$ being greater than $P_g^*$.³

**Model:** Let $Y_1 = 1$ if the compound is selected for clinical trials, 0 otherwise. Therefore the probability of selection is $Pr(Y_1 = 1) = Pr(P_g > P_g^*)$. Let $Y_2 = 1$ if the project succeeds if selected for trial, and 0 if it fails in clinicals, so that $Pr(Y_2 = 1) = E(P_g \mid P_g > P_g^*)$. To estimate the model, we assume that the log of the odds ratio, $\ln(P_g/(1-P_g))$, is normally distributed with mean $\mu$ and unit variance. Further, we assume that $\mu$ depends linearly on a set of independent variables $Z$, i.e. $\mu = Z\gamma$. The threshold $P_g^*$ is assumed to be a function of a set of independent variables $X$. Since $P_g^*$ must be between 0 and 1, we assume $P_g^* = \exp(X\beta)/(1+\exp(X\beta))$ so that $\ln(P_g^*/(1-P_g^*)) = X\beta$. We maximize the following log-likelihood function:

$$L(\beta, \gamma) = \sum_{Y_1=0} Pr(Y_1 = 0) + \sum_{Y_1 = 1, Y_2 = 0} Pr(Y_1 = 1 \& Y_2 = 0) + \sum_{Y_1 = 1, Y_2 = 1} Pr(Y_1 = 1 \& Y_2 = 1) + \sum_{Y_1 = 1, Y_2 = .} Pr(Y_1 = 1 \& Y_2 = .) \tag{1}$$

Where the four terms correspond to: not selected; selected but failed; selected and succeeded; and selected and still in trial, respectively. Note that we have two binary dependent variables, and we are estimating the drivers of $P_g^*$ and $\mu$, rather than the more typical exercise of estimating the probability of selection and the probability of success conditional on selection. The probability of selection is:

$$Pr(Y_1 = 1) = Pr(P_g > P_g^*) = Pr\left( \ln \frac{P_g}{1-P_g} > \ln \frac{P_g^*}{1-P_g^*} \right) = 1 - \Phi(X\beta - Z\gamma) \tag{2}$$

Whereas the probability of success is:

³A different model would be to start with some projects being “good” and others “bad”, with a real valued signal, $P_g$, about whether the project is good. Instead, here we consider each project to be like a coin toss with the probability of success (“heads”) equal to $P_g$. The firm observes $P_g$ and then decides whether it wants to toss the coin.
\[
\Pr(Y_2 = 1 | Y_1 = 1) = E[P_g | P_g > P_g^*] = \int_{P_g^*} P_g f(P_g | P_g > P_g^*) dP_g = \frac{1}{1 - \Phi(X\beta - Z\gamma)} \int_{P_g^*} P_g f(P_g) dP_g \quad (3)
\]

Danzon et al. (2005) effectively estimate \( \Pr(Y_2 = 1 | Y_1 = 1) \). Although they acknowledge the selection issue by including the share of projects selected from pre-clinicals in that indication as a regressor, they cannot separately identify \( \gamma \) and \( \beta \). Nerkar (2003) and Chandy et al. (2006) estimate \( \Pr(Y_1=1 \& Y_2=1) \equiv \Pr(Y_2 = 1 | Y_1 = 1) \Pr(Y_1=1) \). All else equal, as a firm becomes more selective (the second term decreases), the compounds it advances into clinicals will be more likely to succeed (the first term increases), but the product of the two, the share of compounds in pre-clinicals that eventually succeed, may either fall or rise.

Without modeling both \( \Pr(Y_2 = 1 | Y_1 = 1) \) and \( \Pr(Y_1=1) \), and without explicitly recognizing the interdependence between them, one cannot distinguish innovativeness (i.e., \( \mu \)) across firms.

4. Hypothesis development

4.1 Hypotheses about selection

We define a firm to be more selective in a therapeutic area if \( P_g^* \) is higher. There are many factors that condition \( P_g^* \): Firm scale and scope, product cannibalization concerns, differences in organizational capability and incentives of firms, and variation in market profitability across therapeutic areas.

We start with the classical scale and scope factors. We distinguish between scale at the level of the research program and scale at the level of the firm. Program-level economies of scale reduce development costs, and hence, lower \( P_g^* \). For example, a company with long-standing arrangements with academic hospitals for trials in an indication will find it easier to develop another compound within that indication than in others. In addition, spillovers are more extensive: the results for a given compound can be informative for other compounds in the same indication. This implies a lower D and a higher V, and a lower \( P_g^* \). Scale at the level of the firm has different implications. A firm engaged in more clinical trials may face capacity constraints. Bringing an additional compound will imply higher incremental cost of development (higher D), and thus the firm will enter new compounds in clinical trials only if they are promising, i.e., \( P_g^* \) will be higher. Finally, scope, i.e., a wider diversification of projects across research areas, may increase value and reduce development costs because of spillovers across research programs.
as Henderson and Cockburn (1996) suggested. This will make the firm less selective. Formally, we state the following hypothesis.

**Hypothesis 1a.** Research scale at the level of the program makes the firm less selective (lower $P_g^*$).

**Hypothesis 1b.** Research scale at the level of the firm makes it more selective (higher $P_g^*$).

**Hypothesis 1c.** A wider scope across the firm’s research areas makes it less selective (lower $P_g^*$).

A well known feature of the pharmaceutical industry is that it is populated by two fundamentally different types of firms, the established pharmaceutical producers and the biotechnology companies. The established drug firms were founded early in the 20th century, if not earlier. A large gap separates the entry of the pharmaceutical firms and the first biotech company, Genentech, in 1976. Syntex, the youngest research based US pharmaceutical company before Genentech, was founded in 1958. Waves of biotech companies have entered after Genentech. Their main driver has been research, and the comparative advantages and specialization of these firms are clearly upstream compared to the drug manufacturers (Gambardella, 1995). Such differences in origin, time of entry and development underlie profound differences between these two company types.

For example, Arrow’s (1962) suggests that the fear of cannibalizing the profits from existing markets and products leads an incumbent firm to under-invest in research. In large established firms, new compounds are more likely to cannibalize existing products. By contrast, most biotech firms have no products on the market and have little to fear about cannibalization of existing products. Insofar as one cannot fully control for this effect in the empirical analysis, the cannibalization effect is an important reason to distinguish between different firm types. Difficult-to-measure differences in organizational capabilities are another reason to distinguish between biotech and pharmaceutical firms. Interviews with managers reveal that pharmaceutical firms have well established routines and financial models for deciding how compounds are moved along through the various stages of pre-clinical research and clinical research. By contrast, many of the smaller entrants lack such discipline, and the founders may have
strong biases that favor compounds being selected. The need to provide “good news” to investors may also bias startups to push drugs into clinical trials (Guedj and Scharfstein, 2005).

In addition, there may be differences in risk aversion. Ordinarily, one might imagine that large established firms would be less risk averse. However, as Stiglitz and Weiss (1981) showed in a seminal paper, limited liability laws may make startups more risk loving, particularly in taking large risks that might result in bankruptcy. The intuition is simple. A large risk (“swinging for the fences”) has high reward but also a high cost in terms of bankruptcy. However, with few assets to protect, and with outside equity investors frequently having a large share of the capital at risk if the project (and the firm) fails, managers of small biotech firms may be inclined to swing for the fences, which implies that they would have a lower $P_g^*$. Indeed, using patent citation analysis, Owen-Smith and Powell (2006) find that biotech firms in the Bay Area, which has a higher involvement of VC firms, are more likely to initiate riskier projects, than biotech firms in the Boston region, where universities (and NIH funding) are more heavily represented. Interviews with R&D executives support the idea that biotech firms tend to push compounds into clinical development that firms with bigger product portfolios might hold back. When asked, the managers also believe that biotech firms are more inclined to swing for the fences.

Among the biotech firms themselves, there are distinctions to be made. Some of the early founded biotech firms that survive today, such as Genentech and Amgen, have become similar to the established drug companies. They have products in the market and they have to manage cannibalization. They have strong financial models for selecting projects, and also considerable wealth at risk from an expensive failure. This suggests that the $P_g^*$ of the older biotech firms lies somewhere between that of established pharmaceutical firms and that of the smaller, more recent biotech entrants.\(^4\) We can then formulate the following hypothesis.

\(^4\) Clearly, selection effects are at work here as well. The biotech firms that entered early and have survived are more efficient, reinforcing the argument that they have become more similar to the established companies.
Hypothesis 2. Even after controlling for the scale and scope of research, established pharmaceutical companies are more selective (higher $P_{g^*}$) than the biotech firms. The older and more established biotech firms are more selective than the younger biotech firms.

4.2 Hypotheses about performance

Below we use the expression “higher innovation performance” to mean a better distribution of the probability of success for compounds discovered in preclinical research, i.e., a higher $\mu$.

Henderson and Cockburn (1996) identify three types of economies in research: i) economies of scale at the level of the research program; ii) economies of scale at the level of the firm; iii) economies of scope across research programs of the firm (see also Macher and Boerner 2006; Nerkar and Roberts 2004). There are a variety of sources of scale and scope economies. A larger firm with a diverse research portfolio may have a larger chemical library (Thomke and Kuehnerle 2002); it may be more knowledgeable about the underlying biochemical processes; it may have better models for interpreting results from animal and small sample human studies; or it may be better able to modify the original compound to improve its efficacy and reduce its side effects.

These benefits may be offset by organizations that are maladapted, with perverse incentives and inadequate feedbacks (e.g., Nerkar, 2003). There is, however, another reason why measures of program level economies may appear to result in lower $\mu$. A firm with a number of compounds in trial for the same indication is unlikely to commercialize all of them, even if they could all get FDA approval. Instead, it will pick the most promising amongst them. Though our formal model assumes that once selected, compounds progress through clinical trials based entirely on technical merits, this is a simplification. In reality, firms may choose to bring a number of promising compounds into trial for an indication, but pick only the best, terminating the rest (Dahan and Mendelson, 2001). The cannibalization effect may work similarly. A firm with a product may choose not to commercialize a drug that is safe and effective but very similar in its target market to the existing product. Put differently, the portfolio and cannibalization effects do not reduce $\mu$. However, they result in an estimated $\mu$ that is lower than the true $\mu$.  

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Hypothesis 3. The innovation performance of a firm in a given research area increases with a) the overall research scale of the firm; b) the span of the research across research areas (scope); c) research scale at the level of the program. The portfolio and cannibalization effects reduce the measured innovation performance.

As with selection, there are other differences between established firms and biotech companies that may affect performance. There is a substantial literature arguing that smaller research-intensive companies are more creative than established firms. For example, smaller firms are said to have a more open environments, enhancing benefits from external knowledge (e.g., Chesbrough, 2003) and are less prone to asymmetric information between managers and inventors inside the organization, (Arrow, 1983; Holmstrom, 1989). Conversely, internal bureaucracies inside large firms may crush good ideas. Also, larger firms may tend to “rest on one’s laurels” (Christensen 1997), and they may stress exploitation rather than exploration (Levinthal and March 1993).

However, an alternative hypothesis has the opposite prediction. The agency model in Guedj and Scharfstein (2005), and the idea that small biotech firms may have excessive incentives for risk bearing imply that biotech firms would advance even inferior compounds into clinicals. In terms of our model, this implies a lower estimated $\mu$ for biotech firms. Ultimately, the net effect of these two forces is an empirical matter. We then formulate two alternative hypotheses.

Hypothesis 4: Biotech companies have higher innovation performance than the established pharmaceutical firm because smaller organizations are more innovative.

Hypothesis 4’: Biotech firms have lower innovation performance because of misaligned incentives.

4.3 Licensing related hypotheses

If the licensing agreement does not share costs and benefits in the same proportion across the licensee and licensor, this will bias the selection threshold. In the extreme case, if the licensee is responsible for the cost of development but has to pay a royalty from sales of a successful compound to the licensor, this effectively reduces $V$ for the licensee, implying a lower $P_g^*$. However, knowing this, partners try to align
incentives by sharing costs and benefits. We do not observe details of the licensing contracts and accordingly we do not formulate a hypothesis regarding the effect of licensing on \( \text{Pg}^* \).

Regarding the performance of licensed compounds, following Akerlof (1970), the economics literature predicts that markets for knowledge are characterized by information asymmetries about the quality of the technology offered for license (Zeckhauser, 1996). Although these arguments are typically used support the contention that licensing is not the preferred mode of commercialization, they can be extended to performance, as Pisano (1997) does in the pharmaceutical industry context. The notion is that a licensor is likely to keep its most promising technologies for its own use and only offer inferior ones for license. Licensees therefore believe that compounds offered for licensing are on average worse than compounds not offered for license, conditional on observable characteristics. If so, the licensees must be offered a discount. But then the suppliers of good compounds are less likely to offer their compounds for license, thereby fulfilling the belief about compounds offered for license being inferior. If so, licensed compounds will be drawn from an inferior distributions (lower \( \mu \)) than those retained for in-house development. Guedj (2005) also offers an asymmetric-information based model which implies that licensed compounds have lower \( \text{Pg}^* \) but also lower probability of success. He finds empirical support in a sample of projects selected for clinicals.

There are however some countervailing arguments suggesting that the market for lemon is not an important problem in technology markets. Arora and Gambardella (1994), building on the insights of Cohen and Levinthal (1989) and Rosenberg (1990), argue that research capabilities also provide firms with the ability to evaluate external technologies. Licensees in the drug industry are typically firms that perform research themselves, so that potential buyers are capable of evaluating the technical characteristics of the licensed compound, especially since strong patent protection in this industry facilitates the disclosure of the relevant information. Furthermore, many licensing transactions are embedded in strategic research partnerships, involve minority investments or co-development deals, reducing, if not eliminating, potential information asymmetries. Thus, the null to the hypothesis below is
that the innovation performance of the licensed compounds is not different from those developed internally.

**Hypothesis 5** *(market for lemons).* Licensed compounds exhibit lower innovation performance than internally developed compounds.

5. **Description of the data**

Our sample is drawn from the ATA database (ATAdb), which combines proprietary datasets on the pharmaceutical industry. It reports information about more than 17,000 R&D projects all over the world carried over since the 1980s.\(^5\) Following Danzon et al. (2005), we consider each indication for which the compound is being developed as a separate project. Also, countries have different institutions and procedures for advancing compounds to the clinical trials, and for approving them for sales. Even in our database both the selection and success rates of European trials are higher than the US, which suggests that the US criteria are more stringent. To reduce this source of heterogeneity we focus on US trials. Since our database indicates where the preclinical research is conducted, our sample is composed of all the projects with preclinical research in the US (whether by US firms or not). We classify as “selected” those projects that start clinical I in the US, and analogously for successful projects.\(^6\) We exclude projects originated by hospitals, public sector labs or universities, where selection processes may be different. We reduce the censoring problem posed by the ongoing projects that are neither successes nor failures by including only the projects that enter the preclinical trials between 1980 and 1994.\(^7\) Our final sample is composed of 3,311 projects.\(^8\)

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5 The names of the firms in the database are reported as they are in 2002. Therefore we cannot consider separately the projects of the major pharmaceutical firms that merged or were acquired during the 1990s.

6 There are a few cases with missing information about the location of preclinical research, which we dealt with case by case, by using other contextual information in the database.

7 Following Danzon et al. (2005), we classify as failure a project that remains in a phase, without any further reported events, for longer than the maximum number of years observed for completion of each phase in the non-censored sample. The maximum number of years is computed within each indication. When this is not practicable – due to missing observation for the indication – we consider the maximum over all the indications.

8 By selecting trials started between 1980 and 1994, the sample reduces to 8,107 observations, of which 7,247 started by pharmaceutical and biotechnology firms. We further exclude the projects co-developed by two or more institutions, leaving us with 6,659 observations. By focusing only on preclinical research projects undertaken in the US and projects with identifiable outcomes, we end up with 3,311 observations.
We divide biotech firms into two types, depending upon whether they were founded before or after 1988, the median founding year for the biotech firms in our sample. We also distinguish between the top pharmaceutical corporations worldwide (henceforth “Established Pharma”), and smaller pharmaceutical firms developing compounds that target predominantly infection and inflammation, asthma and diabetes, obesity and sexual dysfunctions (henceforth “Other Pharma”), which are typically much less R&D intensive. Specifically, we distinguish among the following four types of companies:

i) **Pioneer Biotech.** Firms, founded before 1988, that apply biotechnological methods to the discovery and development of new drugs.

ii) **Other Biotech.** All other firms using biotechnology for the discovery of new drugs.

iii) **Established Pharma.** Pharmaceutical firms that are among the top 50 firms worldwide by sales for at least 10 years during the 15 year period 1983-1998 (excluding biotech firms and adjusting for mergers and missing data for 1995).

iv) **Other Pharma.** All other pharmaceutical firms.

### Table 1: Firm types and R&D projects

<table>
<thead>
<tr>
<th>Firm Type</th>
<th>Number of Projects (%)</th>
<th>Number of different firms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioneer Biotech</td>
<td>1,031 (31.14%)</td>
<td>123 (37.39%)</td>
</tr>
<tr>
<td>Other Biotech</td>
<td>556 (16.79%)</td>
<td>101 (30.70%)</td>
</tr>
<tr>
<td>Established Pharma</td>
<td>1,512 (16.79%)</td>
<td>31 (9.42%)</td>
</tr>
<tr>
<td>Other Pharma</td>
<td>212 (6.40%)</td>
<td>74 (22.49%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3,311 (100%)</strong></td>
<td><strong>329 (100%)</strong></td>
</tr>
</tbody>
</table>

Table 1 reports information on the number and projects related to the four types of firms that we considered in the analysis. Our empirical measures are summarized in Table 2. Measures that vary across firms and indication are noted as measured at the project level, while others vary only across firms, or only across indications. Table 2 also indicates the predicted sign of the variable. Some variables are excluded from $\mu$ (and the corresponding cell is left blank), while other variables are used as controls (and the corresponding cell merely has a ✓ mark, rather than a + or a − mark).

**Scale and Scope.** We measure `scale_program`, or the scale at the program level by the total number of projects started by the firm for the given indication. `Scale_firm`, or scale at the level of the firm is...
measured by the total number of ongoing projects for the firm. Scope is measured by Herfindahl index of diversification of projects across indications, for the firm. These measures are based on the literature. Danzon et al. (2005) and Abrantes-Metz (2003) use the number of drugs in development to measure overall firm scale. To measure program level economies, Macher and Berner (2006) use the number of projects completed and Danzon et al. (2005) use the total number of projects in the therapeutic area. Finally, Danzon et al. (2005) use the same herfindal index based measure that we use, and Macher and Boerner (2006) use the number of therapeutic areas in which the firm is active to measure scope economies. Henderson and Cockburn (1996) use the concentration of R&D expenditures, which we cannot do because we lack R&D data at the program level.

**Licensed Compounds:** The database records the licensor and each licensee. We considered a project as “licensed” only if the agreement was signed in pre-clinicals.

**Project Controls.** We develop a number of binary, indication level indicators: (i) whether the disease is lethal or not (lethal), (ii) whether it can result in organ damage or complications (organ damage), (iii) whether the disease is chronic or acute (chronic), (iv) whether the disease has multiple causes or not (multiple causes), and (v) if the disease targeted is rare or not (rare). These factors condition both the selection threshold, \( P^*_g \), and, \( \mu \), the average probability of success.

We also use an indicator for whether the firm already has a product in the ATC2 market. Our measure of scale at the level of the program is the cumulative number of past projects for that indication.

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9 When multiple licensees are present, we assign the development of the project to the largest US firm. We then inspected this assignment to make sure that we consider the firm that was actually in charge of the R&D development of the project.

10 Indication and ATC are two complementary classification systems. For instance, A02 is the ATC2 code for drugs for acid related disorders, where the corresponding indication may be “heartburn”. As this suggests, ATC deals with the therapy, using the anatomy as the main organizing theme. Indications focus on the clinical symptoms for which the drug is being tested. The main source for the disease information is Braunwald et al. (2001). Other information comes from e-medicine reviews from the disease database (http://www.diseasedatabase.com). For diffusion data, we obtain information from the “rare disease database” cited by the FDA, and available at http://rarediseases.about.com/cs/orphandrugs/a/122103.htm.

11 Multiple causes = 1 if the etiology is multifactorial and = 0 if it is unknown or single factor.

12 An orphan or rare disease affects fewer than 200,000 individuals in the United States. The “Orphan Drug Act” (1983) allows drug companies to take tax deductions for about three-quarters of the cost of the clinical studies (FDA, 1999), with an implied reduction of cost for development.
Since we want Scale_Program to account for research scale and experience in the program we need to control for for the scale or experience of the firm associated with the commercialization of products in the same area, viz. downstream factors rather than research.\footnote{We also employ the total number of molecules in the same ATC2 with no change in result. We prefer a dummy indicator because the number of commercialized molecules is very skewed (average 0.7, maximum 55, 95% of the observations equal or smaller than to 4).}

**Table 2: Variables in the estimated equations**

<table>
<thead>
<tr>
<th>$P_{g*}$</th>
<th>$\mu$</th>
<th>Variable</th>
<th>Measured as</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>+</td>
<td>Scale_Program (project)</td>
<td>Number of projects already started by the firm for that indication</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>Scale_Firm (firm)</td>
<td>Total number of projects by the firm</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>Scope (firm)</td>
<td>Herfindahl index of firm’s projects across indications</td>
</tr>
<tr>
<td>✓</td>
<td>-</td>
<td>Compound licensed (project)</td>
<td>If the compound licensed in preclinical</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>Closeness to science (project)</td>
<td>Share of projects jointly developed with a public research organization for that indication</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>Presence in ATC2 product market (project)</td>
<td>= 1 if firm has a product in the ATC2 class, = 0 otherwise</td>
</tr>
<tr>
<td>-</td>
<td></td>
<td>Public (firm)</td>
<td>= 1 if firm is public when the project is started</td>
</tr>
<tr>
<td>-</td>
<td></td>
<td>Market Size (indication)</td>
<td>Worldwide sales in the ATC2 class</td>
</tr>
<tr>
<td>+</td>
<td></td>
<td>Market Competition (indication)</td>
<td>1. Log of the number of firms with a product in the ATC2 class</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disease Characteristics (indication)</td>
<td>2. Share of established pharma witha product in the ATC2 class.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lethal, organ damage, multi-causal, chronic, rare, first-in-class (see text)</td>
</tr>
</tbody>
</table>

Finally, since pharmaceutical and biotech firms may choose projects with different levels of innovativeness or risk, we devise a proxy for the level of innovativeness (and therefore of risk) associated to the project. We use the information whether the compound is first-in-class or a follower molecule (*first in class*).\footnote{Other things being equal, we expect first-in-class compounds to exhibit a lower selection threshold. This is because there are fewer alternatives available, and hence they have to overcome a lower hurdle to improve upon existing remedies. We also expect them to be drawn from a worse distribution because there is less information about potential side effects. Unfortunately, in almost 40% of the cases it is not possible to classify the molecule under study because of the lack of information about its chemical characteristics. We create an indicator variable, *First-in-class unknown*, that codes for when this information is missing.} Other things being equal, we expect first-in-class compounds to exhibit a lower selection threshold. This is because there are fewer alternatives available, and hence they have to overcome a lower hurdle to improve upon existing remedies. We also expect them to be drawn from a worse distribution because there is less information about potential side effects. Unfortunately, in almost 40% of the cases it is not possible to classify the molecule under study because of the lack of information about its chemical characteristics. We create an indicator variable, *First-in-class unknown*, that codes for when this information is missing. Through the use of these fine grained controls at the level of indication, we
can avoid using indication fixed effects, which can bias non-linear estimates, a possibility confirmed by (unreported) Monte Carlo simulations.

**Economic characteristics of therapeutic area:** We use information on the worldwide sales (at the Anatomic Therapeutic Classification at the 2\textsuperscript{nd} digit level, ATC2) in the year the project is started, as a proxy for \(V\).\textsuperscript{15} We measure the degree of competition by the number of firms operating in that indication (world wide) at the time the project is launched. We also employ the share of established pharmaceutical firms as an additional control for the intensity of competition. We use the share of projects developed with universities, as a measure of the firm’s links with research institutes, and its closeness to science (closeness to science).

### Table 3: Descriptive Statistics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>S.D.</th>
<th>Min.</th>
<th>Max</th>
<th>Variable</th>
<th>Mean</th>
<th>S.D.</th>
<th>Min.</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection</td>
<td>0.48</td>
<td>0.50</td>
<td>0</td>
<td>1</td>
<td>Closeness to Sc.</td>
<td>0.05</td>
<td>0.16</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Success</td>
<td>0.34</td>
<td>0.48</td>
<td>0</td>
<td>1</td>
<td>Public Firm</td>
<td>0.84</td>
<td>0.37</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pioneer Biotech</td>
<td>0.31</td>
<td>0.46</td>
<td>0</td>
<td>1</td>
<td>Market Size</td>
<td>2.38</td>
<td>2.47</td>
<td>0</td>
<td>14.4</td>
</tr>
<tr>
<td>Established Pharma</td>
<td>0.46</td>
<td>0.50</td>
<td>0</td>
<td>1</td>
<td>Log Competitors</td>
<td>3.09</td>
<td>1.02</td>
<td>0</td>
<td>5.23</td>
</tr>
<tr>
<td>Other Biotech</td>
<td>0.17</td>
<td>0.37</td>
<td>0</td>
<td>1</td>
<td>Share of EC firms</td>
<td>0.28</td>
<td>0.18</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other Pharma</td>
<td>0.06</td>
<td>0.24</td>
<td>0</td>
<td>1</td>
<td>First-in-class</td>
<td>0.30</td>
<td>0.46</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Scale_Project</td>
<td>2.67</td>
<td>3.53</td>
<td>0</td>
<td>31</td>
<td>First-in-class unknown</td>
<td>0.39</td>
<td>0.49</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Scale_Firm</td>
<td>36.23</td>
<td>46.19</td>
<td>0</td>
<td>586</td>
<td>Lethal</td>
<td>0.75</td>
<td>0.43</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Scope</td>
<td>0.83</td>
<td>0.21</td>
<td>0</td>
<td>0.98</td>
<td>Organ Damage</td>
<td>0.78</td>
<td>0.42</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Presence in ATC2 Product</td>
<td>0.18</td>
<td>0.39</td>
<td>0</td>
<td>1</td>
<td>Multiple causes</td>
<td>0.80</td>
<td>0.40</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>License (preclinical only)</td>
<td>0.08</td>
<td>0.27</td>
<td>0</td>
<td>1</td>
<td>Chronic</td>
<td>0.79</td>
<td>0.40</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rare</td>
<td>0.04</td>
<td>0.20</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Specification and identification of \(\text{P}_{g*}\) and \(\mu\).** The system of equations we estimate is non-linear. We also impose three exclusion restrictions: We assume that the economic characteristics of the compound, i.e., the size of the market, the level of competition in the market, and whether the firm is private or public, only affect the selection threshold and not distribution of the probability of success. This is how we identify selection (\(\text{P}_{g*}\)) as opposed to performance (\(\mu\)). Second, recall that we normalize the variance.

\textsuperscript{14} The information about the chemical name of the projects and its Chemical Abstract Service (CAS) registry number (when available) has been employed to distinguish me-too and second-generation molecules from first-in-class compounds (see Reddy 2003).
of \ln(P_g/(1-P_g)) to unity. We do allow for inter-dependence across the observations for a firm by reported standard errors that are clustered at the firm level. Table 3 presents the descriptive statistics.

6. Empirical results

Table 4 presents simple probit estimates of the selection and success equations estimated separately. Compared to established pharmaceutical firms, biotech firms are less likely to take compounds into clinical trials (they have a lower probability of selection) and have a lower probability of success, though the difference is not statistically significant. Firm scale increases the probability of success (though it leaves selection probability unchanged), whereas program scale decreases both selection and success probability, and scope reduces selection and success. Projects for more profitable markets (larger size and lower competition) have higher probability of selection and success. The presence of downstream assets (a product already in the market) makes selection more likely but reduces success.

It is tempting to try to interpret these results in terms of the various theories about differences across firms or firm scale and scope. However, as we discussed in developing our model, the probability of success will also depend upon the selection threshold, and vice versa. For instance, is scope associated with higher success because it is associated with lower selection probability? If so, should program scale (associated with lower success probability) have been associated with greater selection probability? This is difficult to reconcile with a simple selection model à la Heckman, in which the same underlying process drives both selection and success.

In other words, we need to estimate the structural parameters. Table 5 reports the results obtained from estimating the model described in Section 3, using STATA. Note that while table 4 reports the drivers of the probability of selection and success, table 5 reports the drivers of the selection threshold and the innovative performance. For instance, the coefficients reported under probability of selection in table 4 are \( \beta - \gamma \), whereas table 5 reports \( \beta \). We estimate two specifications. In one, we only use the firm type

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15 We use 1983 figures for projects started in 1980-82 as well, because data for those years are missing.
dummies (Established Pharma is the reference group) and disease controls, while in the second we also include measures of scale and scope and firm and market controls.

### Table 4: Probit estimates

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pr Selection</td>
<td>Pr Success</td>
</tr>
<tr>
<td>Pioneer Biotech</td>
<td>-0.31** (0.11)</td>
<td>-0.22 (0.15)</td>
</tr>
<tr>
<td>Other Biotech</td>
<td>-0.47** (0.13)</td>
<td>-0.79** (0.36)</td>
</tr>
<tr>
<td>Other Pharma</td>
<td>-0.18 (0.17)</td>
<td>0.53** (0.20)</td>
</tr>
<tr>
<td>License (precl)</td>
<td>0.03 (0.15)</td>
<td>0.14 (0.28)</td>
</tr>
<tr>
<td>Scale_Program</td>
<td>-0.09** (0.02)</td>
<td>-0.14** (0.03)</td>
</tr>
<tr>
<td>Scale_Firm</td>
<td>-.1E-4 (.1E-2)</td>
<td>0.01** (.2E-2)</td>
</tr>
<tr>
<td>Closeness to science</td>
<td>0.59** (0.25)</td>
<td>.4E-2 (0.23)</td>
</tr>
<tr>
<td>Presence in ATC2 class</td>
<td>0.29** (0.12)</td>
<td>-0.3** (0.12)</td>
</tr>
<tr>
<td>Public</td>
<td>0.17 (0.11)</td>
<td>0.04 (0.20)</td>
</tr>
<tr>
<td># Competitors (log)</td>
<td>-0.14** (0.04)</td>
<td>-0.15** (0.07)</td>
</tr>
<tr>
<td>% established pharma competitors</td>
<td>0.36 (0.22)</td>
<td>0.18 (0.24)</td>
</tr>
<tr>
<td>Market Size</td>
<td>0.02 (0.02)</td>
<td>0.1** (0.02)</td>
</tr>
<tr>
<td>Lethal</td>
<td>0.07 (0.09)</td>
<td>-0.13 (0.14)</td>
</tr>
<tr>
<td>Organ Damage</td>
<td>-0.17** (0.08)</td>
<td>0.13 (0.09)</td>
</tr>
<tr>
<td>Multiple causes</td>
<td>-0.12 (0.08)</td>
<td>-0.20* (0.11)</td>
</tr>
<tr>
<td>Chronic</td>
<td>0.02 (0.07)</td>
<td>-0.13 (0.15)</td>
</tr>
<tr>
<td>Rare</td>
<td>-0.12 (0.15)</td>
<td>0.73** (0.2)</td>
</tr>
<tr>
<td>First in class</td>
<td>-0.36** (0.10)</td>
<td>-0.20 (0.15)</td>
</tr>
<tr>
<td>First in class unknown</td>
<td>-1.47** (0.09)</td>
<td>-1.54** (0.24)</td>
</tr>
<tr>
<td>Constant</td>
<td>0.97** (0.14)</td>
<td>0.09 (0.21)</td>
</tr>
<tr>
<td>Obs.</td>
<td>3.311</td>
<td>1.088</td>
</tr>
<tr>
<td>Log-likelihood</td>
<td>-1849.98</td>
<td>-616.08</td>
</tr>
</tbody>
</table>

Robust standard errors in parenthesis (clustered by firms). ** denotes p < 5%; * p < 10%.

**Results about selection.** We find that research scale at the program level reduces the selection threshold whereas research scale at the level of the firm as a whole increases the selection threshold, consistently with Hypotheses 1a and 1b. Contrary to previous findings (and to hypothesis 1c), we find that scope makes firms more selective. Other Biotech and Other Pharma exhibit, respectively, a lower and a higher threshold than the Established Pharma. The high selection threshold of Other Pharma, relative to Established Pharma, suggests that the former have higher development costs than the latter, perhaps because Other Pharma lack substantial production and marketing assets. By contrast, there is little difference in the selection process between the Pioneer Biotech and the Established Pharma – the older
biotech firms have grown similar to the established firms. However, the coefficient of the Other Biotech dummy is sizable (ranging from -1.25 to -1.15); even after controlling for differences in scale, scope and downstream assets. Younger biotech firms have lower selection thresholds, consistent with theories about greater risk appetites, potential agency problems, and weaker management models. This corroborates Hypothesis 2.

Table 5: Structural Model, Maximum Likelihood Estimates

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pg*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioneer Biotech</td>
<td>-0.26 (0.32)</td>
<td>-0.56* (0.31)</td>
</tr>
<tr>
<td>Other Biotech</td>
<td>-1.25* (0.71)</td>
<td>-1.72*** (0.70)</td>
</tr>
<tr>
<td>Other Pharma</td>
<td>1.04** (0.40)</td>
<td>0.86** (0.42)</td>
</tr>
<tr>
<td>License</td>
<td>0.24 (0.41)</td>
<td>0.27 (0.45)</td>
</tr>
<tr>
<td>Scale_Program</td>
<td>-0.20** (0.04)</td>
<td>-0.29** (0.04)</td>
</tr>
<tr>
<td>Scale_Firm</td>
<td>0.01** (.6E-4)</td>
<td>0.01** (.1E-2)</td>
</tr>
<tr>
<td>Closeness to science</td>
<td>-0.20 (0.26)</td>
<td>0.39 (0.30)</td>
</tr>
<tr>
<td>Presence in ATC2 class</td>
<td>-0.71** (0.21)</td>
<td>-0.42** (0.18)</td>
</tr>
<tr>
<td>Public</td>
<td>-0.17 (0.11)</td>
<td></td>
</tr>
<tr>
<td>% establish pharma competi torque</td>
<td>0.13** (0.04)</td>
<td></td>
</tr>
<tr>
<td>Market Size</td>
<td>-0.01 (0.02)</td>
<td></td>
</tr>
<tr>
<td>Lethal</td>
<td>-0.26 (0.25)</td>
<td>-0.19 (0.24)</td>
</tr>
<tr>
<td>Organ Damage</td>
<td>0.31* (0.17)</td>
<td>0.14 (0.17)</td>
</tr>
<tr>
<td>Multiple causes</td>
<td>-0.30 (0.22)</td>
<td>-0.42** (0.18)</td>
</tr>
<tr>
<td>Chronic</td>
<td>-0.23 (0.27)</td>
<td>-0.20 (0.28)</td>
</tr>
<tr>
<td>Rare</td>
<td>1.34** (0.30)</td>
<td>1.22** (0.33)</td>
</tr>
<tr>
<td>First in class</td>
<td>-0.19 (0.29)</td>
<td>-0.54* (0.28)</td>
</tr>
<tr>
<td>First in class unknown</td>
<td>-2.32** (0.54)</td>
<td>-3.79** (0.58)</td>
</tr>
<tr>
<td>Constant</td>
<td>-1.07** (0.38)</td>
<td>-0.10 (0.37)</td>
</tr>
<tr>
<td>Obs.</td>
<td>3,311</td>
<td>3,311</td>
</tr>
<tr>
<td>Log-likelihood</td>
<td>-2467.54</td>
<td>-2345.18</td>
</tr>
</tbody>
</table>

Robust standard errors in parenthesis (clustered by firms). ** denotes p < 5%; * p < 10%.

As far as our controls are concerned, the number of competitors, as a measure of the profitability of the market, has the expected effects (increase Pg*). Similarly, previous commercial experience in the ATC2 class reduces Pg*, which suggests higher economic value from successful compounds because of existing commercialization capabilities in the area or other related learning factors.
Results about performance: Table 5 shows that scale at the program level reduces $\mu$ but overall research scale at the firm level increases this probability. The effect of scope is positive, but imprecisely measured. Thus, Hypothesis 3 is only partially supported. If we believe that program (indication) level research economies are in fact significant and positive, then our measure is confounding economies of scale with the portfolio effect. Consistently, we find that if a firm has a product in the market, $\mu$ is lower, which is surprising if one believes that past experience should improve innovative performance. The alternative explanation appeals to the portfolio effect. To ensure that its downstream assets are fully utilized, a firm with downstream assets in a market will often have more compounds in clinical trials for the same indication (e.g. Higgins and Rodriguez, 2006; Dahan and Mendelson, 2001). However, it will commercialize at most one of the compounds, even if more could gain FDA approval. The higher failure when there are more projects under development for the same indication may simply reflect such portfolio effects.

The important results of Table 5 are that both Pioneer Biotech and Other Biotech have lower $\mu$, implying that they have lower innovative performance compared to Established Pharma, and that Pioneer Biotechs perform better than Other Biotech, even after controlling for scale, scope and downstream assets. Formally, Hypothesis 4 is rejected in favor of the alternative Hypothesis 4'. There are three interpretations, which are not mutually exclusive. The first one is that biotech firms are in fact less innovative than established pharmaceutical firms. The second one is that biotech firms advance into clinical trials less promising compounds, because their managers have perverse incentives, or because they are incapable of correctly evaluating the potential of the compound, or because they are willing to take more risk (which may be related to their incentives, as discussed earlier). The third interpretation is that the regulatory hurdles for the average biotechnology product are more difficult to meet than those for the average pharmaceutical product, and our controls do not adequately control for these differences.

Our final set of results is about the licensed compounds. Recall that the lemons hypothesis is based on the seller systematically offering a lower quality good, keeping the superior quality good for her
own use. In our framework, this implies that licensed compounds have a lower $\mu$ than compounds developed in-house by the licensor. Table 5 shows that we do not observe any market for lemons. Licensed compounds face a higher selection threshold, $P_g^*$, as might be expected if the licensee has to share revenues (but not costs) with the licensor. However, they also have a higher $\mu$, although neither coefficient is statistically significant. Thus, Hypothesis 5 is rejected. The countervailing effects discussed in Section 3 appear to be strong enough to avoid any lemons problem. One implication of these results is that the division of innovative labor (Arora et al., 2001) in the pharmaceutical industry must rely upon differences in comparative (rather than absolute) advantage across biotech firms and pharmaceutical firms. Alternatively, the advantage of biotech firms may lie in researching unexplored avenues, rather than doing better what pharmaceutical firms already do.

7. Discussion and Conclusions

A key takeaway from our analysis is that in comparing the innovation performance of firms, one must pay careful attention to differences in behavior, and to factors, such as incentives, that may drive such differences. We explicitly model one aspect of behavior, namely the decision to select a compound into clinical trials. However, there are other aspects of our results which illustrate the same point, such as our finding of no program-level economies of scale, or that a firm which has past experience in the market (and by inference, has downstream assets), is less successful. These apparently anomalous findings can be reconciled by considering the incentives of firms to ensure the full utilization of downstream assets by selecting a number of compounds into clinical trials, at most one of which is marketed, thereby reducing estimated innovative performance. The problem lies with the measure of program level economies of scale (commonly used in the literature), which confounds the economies of scale with the portfolio effect.

Our results imply that even after controlling for scale and scope of the firm, there are significant differences across different types of firms. These differences reflect both performance and behavior, most notably, selection. The different results in Tables 4 and 5 in the previous section suggest that explicitly modeling selection is important. To see this, compare the results about the firm type dummies for
Specification 2 in the two tables. In Table 4 the dummies for Pioneer Biotech and Other Biotech are negative and significant in the selection equation, but in the success equation the estimates are insignificant. Table 5 shows that they have significantly lower $\mu$ but also lower $P_g^*$. Thus, we conclude that the reason biotech firms are less likely to advance compounds into clinical is because on average they have lower quality compounds compared to average pharmaceutical firms, not because biotech firms are more selective.

Robustness checks: We conduct a series of tests to explore the robustness of our results to changes in the sample, alternative measures of market profitability, and alternative assumptions about the distribution of $P_g$. For brevity, we summarize our results. Details are available from the authors upon request. First, our results are largely unchanged if we expand our sample to include projects initiated in Europe, or by universities and other public research organizations. Similarly, defining an established pharmaceutical firm to be one that appears on the list of the top 50 pharmaceutical firms by sales for three, five or ten years does not materially change our results. Second, although the non-linear specification of our likelihood function contributes to identification, our results do not depend upon it. We also estimate a specification where the log-odds ratio of $P_g$ is uniformly distributed over some subset of the unit interval, with little qualitative change in our results. Finally, our results are robust to some alternative empirical measures. For instance, using the herfindahl index of the market shares in an indication (for the year 2001) to measure competition in the market leads to similar results. Similarly, using sales at the ATC3 level in an indication (albeit for a single year, 2001) to measure market size does not affect our findings.\footnote{To validate our estimation results we also compared our estimated $P_g^*$, which corresponds to the ratio of development costs and expected revenues, with estimates of costs and revenues provided by the existing literature (DiMasi et al., 2003; OTA, 1993; and Grabowski et al., 2002). The estimates of $P_g^*$ obtained from these calculations range from 0.07 to 0.19, compared to our estimated value of 0.11, which is very close to the median. Details of these calculations are available upon request.}

Exploring the implications of our results: Since we estimate structural parameters, we can use them for “what-if” scenarios to provide additional insights into the implications of our estimates. We begin by...
using the estimated coefficients from specification 2 in Table 5 to compute the probability of selection, the unconditional probability of success, the value of $P_g^*$ and $\mu$ for the firm types in our sample.

<table>
<thead>
<tr>
<th>Pr. Selection</th>
<th>Pr. Success</th>
<th>$P_g^*$</th>
<th>$\mu$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.48</td>
<td>0.25</td>
<td>0.12</td>
</tr>
<tr>
<td>Pioneer Biotech</td>
<td>0.44</td>
<td>0.19</td>
<td>0.11</td>
</tr>
<tr>
<td>Established Pharma</td>
<td>0.57</td>
<td>0.27</td>
<td>0.13</td>
</tr>
<tr>
<td>Other Biotech</td>
<td>0.30</td>
<td>0.07</td>
<td>0.03</td>
</tr>
<tr>
<td>Other Pharma</td>
<td>0.55</td>
<td>0.43</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Figures 2 and 3 show the simulated the distributions of $P_g$ for the whole sample and by originator types, using our estimates from specification 2 in Table 5. The distribution of $P_g$ is skewed, with a low number of highly successful projects and a high number of projects with low probability of success. In general, the right tails of the four distributions become fatter as we move from the Other Biotech to Pioneer Biotech, Established Pharma, and Other Pharma. Using the estimated coefficients of specification 2 in Table 5 we also perform some simulation exercises. We first study the effects of changes in firm size.

**Figure 2**: Estimated distribution of $P_g$
Table 7: Simulating an increase in the research scale of the firm (Scale_Firm)

<table>
<thead>
<tr>
<th></th>
<th>Pioneer Biotech</th>
<th>Established Pharma</th>
<th>Other Biotech</th>
<th>Other Pharma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline +1 σ</td>
<td>Baseline +1 σ</td>
<td>Baseline +1 σ</td>
<td>Baseline +1 σ</td>
</tr>
<tr>
<td>Pr Selection</td>
<td>0.44</td>
<td>0.57</td>
<td>0.30</td>
<td>0.55</td>
</tr>
<tr>
<td>Pr Success</td>
<td>0.15</td>
<td>0.22</td>
<td>0.04</td>
<td>0.38</td>
</tr>
<tr>
<td>Pg*</td>
<td>0.11</td>
<td>0.13</td>
<td>0.03</td>
<td>0.31</td>
</tr>
<tr>
<td>µ</td>
<td>-2.97</td>
<td>-2.35</td>
<td>-4.79</td>
<td>-1.04</td>
</tr>
</tbody>
</table>

Table 7 reports the estimated effects of a one-standard-deviation increase in Scale_Firm. When this variable increases Pg* increases. Since µ also increases, the probability of selection increases too. Interestingly, the effects of the firm research scale are rather small. Thus, while Scale_Firm is statistically significant in both the selection and performance equations in Table 5, ultimately its overall effect is small relative to the impact of firm type. As discussed, we believe these firm types reflect different organization structures and strategic behavior. Our empirical results suggest that these differences are important for understanding differences in innovation performance.

Limitations and future research: Our results are from the pharmaceutical sector. This sector is extraordinarily research intensive, and its innovation process over the last three decades has been
transformed, with a much greater role for genetics and molecular biology. These transformations have opened up opportunity for entry. Thus, it is a good test bed for exploring differences in innovation capability between incumbents and entrants. Even so, we focus only on one part of the innovation process, drug development, and arguably the part most favourable to incumbents. A fuller analysis, which also incorporates the more upstream research and discovery process, is left for further research.

Another avenue for additional research has to do with differences in risk aversion. We discussed the impact of risk aversion on the selection process. However, such differences may also be a source of unobserved heterogeneity in conditioning other outcomes. We assume that market size, measures of competition, the presence of downstream assets, whether the molecule is first-in-class or not, as well as the other disease characteristics such as lethality, chronicity, and multiplicity of causes, together control for differences in the potential net revenues. However, it is possible that incumbents show superior performance by trying to hit singles while entrants are swinging for the fences. In economic terms, entrants are willing to take bets with smaller probabilities of success but much higher rewards if successful. By contrast, incumbents have more financial reserves, which also makes them more cautious in terms of how much they are willing to bet on any particular project. From a societal perspective, this is an efficient division of labor. Society enjoys the benefits of experimentation by entrants without unduly risking the valuable capabilities in research, development and marketing of the established incumbents. Though plausible and consistent with our results, this story is inconsistent with the conventional wisdom, which holds that even the incumbents pharmaceutical firms are focusing on blockbusters. We leave this issue for further research.

Our results on licensed compounds point to the benefits of the division of labor between entrants and incumbents. From an econometric viewpoint, we treat licensing as exogenous, because estimating a separate licensing equation (to account for potential endogeneity) will require much more detail about potential licensors and licensees than we currently have. The available evidence suggests that projects that are out-licensed and those that are retained in-house appear to be drawn from very similar distributions. This suggests that endogeneity is unlikely but we cannot be more definitive at this stage.
Another extension would be to allow for interactions across projects carried out by a single firm. In developing our hypotheses we discussed some such interactions, most notably the portfolio effect, discussed earlier. A firm with multiple projects for the same indication will likely commercialize the most promising and abandon others, even perhaps some that could have successfully passed clinical trials. In our estimation, we cluster the errors at the level of the firm, but are unable to cluster at the firm cum indication level. As a result, such interactions may be captured through our measures of scale and scope, leading to potentially confounding results. Future research may explicitly model how a firm chooses among the portfolio of compounds in clinical trials for a particular indication, and how this choice varies with whether it has relevant downstream assets, and with potential for product cannibalization.

Despite these limitations, our paper makes two important contributions. It provides a simple model wherein firms choose which compounds to advance into clinical trials, taking into account the technical promise of the compound, but also economic and commercial considerations. The model also specifies how the observed innovation performance is conditioned by this choice. Our second contribution is to analyze the factors that drive this choice, and in particular, how differences in the underlying innovativeness between established firms and entrants and the differences across them in the incentives to advance compounds in trials drive both their behavior and their innovation performance.
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