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Productivity in Pharmaceutical-Biotechnology R&D: the Role of Experience and Alliances

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Productivity in Pharmaceutical-Biotechnology R&D: the Role of Experience and Alliances

Abstract
Using data on over 900 firms for the period 1988-2000, we estimate the effect on phase-specific biotech and pharmaceutical R&D success rates of a firm's overall experience, its experience in the relevant therapeutic category, the diversification of its experience across categories, the industry's experience in the category, and alliances with large and small firms. We find that success probabilities vary substantially across therapeutic categories and are negatively correlated with mean sales by category, which is consistent with a model of dynamic, competitive entry. Returns to experience are statistically significant but economically small for the relatively straightforward phase 1 trials. We find evidence of large, positive and diminishing returns to a firm's overall experience (across all therapeutic categories) for the larger and more complex late-stage trials that focus on a drug's efficacy. There is some evidence that a drug is more likely to complete phase 3 if developed by firms whose experience is focused rather than broad (diseconomies of scope). There is evidence of positive knowledge spillovers across firms for phase 1. However, for phase 2 and phase 3 the estimated effects of industry-wide experience are negative, which may reflect either higher Food and Drug Administration (FDA) approval standards in crowded therapeutic categories or that firms in such categories must pursue more difficult targets. Products developed in an alliance tend to have a higher probability of success, at least for the more complex phase 2 and phase 3 trials, and particularly if the licensee is a large firm.

Keywords
Pharmaceutical and biotechnology R&D, alliances, economics of scale and scope

Disciplines
Health Economics | Medical Education | Pharmacy and Pharmaceutical Sciences | Regional Economics

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PRODUCTIVITY IN PHARMACEUTICAL-BIOTECHNOLOGY R&D: THE ROLE OF EXPERIENCE AND ALLIANCES

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Productivity in Pharmaceutical Biotechnology R&D: The Role of Experience and Alliances
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ABSTRACT

Using data on over 900 firms for the period 1988-2000, we estimate the effect on phase-specific biotech and pharmaceutical R&D success rates of a firm's overall experience, its experience in the relevant therapeutic category; the diversification of its experience, and alliances with large and small firms. We find that success probabilities vary substantially across therapeutic categories and are negatively correlated with mean sales by category, which is consistent with a model of dynamic, competitive entry. Returns to experience are statistically significant but economically small for the relatively straightforward phase 1 trials. We find evidence of large, positive, and diminishing returns to a firm's overall experience (across all therapeutic categories) for the larger and more complex late-stage trials that focus on a drug's efficacy. There is some evidence that a drug is more likely to complete phase 2 if developed by firms with considerable therapeutic category-specific experience and by firms whose experience is focused rather than broad (diseconomies of scope). Our results confirm that products developed in an alliance tend to have a higher probability of success, at least for the more complex phase 2 and phase 3 trials, and particularly if the licensee is a large firm.

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Introduction

Pharmaceutical firms invest a greater percentage of sales in research and development (R&D) than any other industry. R&D accounted for 15.6 percent of global sales in 2000 for the US research-based pharmaceutical industry, compared to 10.5 percent for the next highest industry (computer software), 8.4 percent for electrical and electronics firms, and 3.9 percent for U.S. companies overall, excluding drugs and medicines (Pharmaceutical Research Manufacturers Association, 2001). The average R&D cost per new chemical entity (NCE) brought to the market is estimated at $802 million (DiMasi, Hansen, and Grabowski, 2002). The cost per NCE is high for three reasons: high input costs for both drug discovery and drug development, including human clinical trials that are required by the Food and Drug Administration (FDA) to establish proof of safety and efficacy;[1] the time value of money considering that it takes 12-15 years to advance a drug from discovery through regulatory approval; and high failure rates, because the cost of "dry holes" – compounds that fail – is included in the average cost per approved NCE. Failure rates during discovery and development are high: for each new compound that is approved, roughly five enter human clinical trials and 250 enter preclinical testing. Thus a key challenge in the management of pharmaceutical and biotech R&D is to increase productivity by improving the percentage of compounds that successfully reach the market and, in particular, to minimize the probability that a compound will fail late in the development process after significant costs have been incurred.

Relatively little is known about the determinants of success rates in pharmaceutical and biotech R&D. This is surprising given the critical importance of success rates in determining the expected cost of an individual drug, the overall cost of and return to pharmaceutical R&D (Grabowski and Vernon, 1994, 2003), and in valuing individual drugs, a company's pipeline of drugs, and a company as a whole. Most

[1] Firms must file an Investigational New Drug application (IND) with the FDA and receive approval before a drug can be taken into human clinical trials. Phase 1 clinical trials test whether the drug is safe in healthy subjects; phase 2 trials test whether the drug is effective in small samples of patients with the target disease; and phase 3 trials test whether the drug is effective in a large sample of patients with the targeted disease. Upon completing phase 3, a

of the published data on pharmaceutical R&D success rates come from the Tufts Center for Drug Development (CSDD), a proprietary database that now contains drug development histories for 24 large pharmaceutical firms. In a series of studies focusing on compounds that entered clinical trials between 1980 and 1992, DiMasi and his colleagues (DiMasi *et al*., 1991; DiMasi, 2000; and DiMasi, 2001) report estimates of the average success rate: by development phase, averaged over all firms; for selected therapeutic categories; and for self-originated versus in-licensed drugs across all therapeutic categories. DiMasi (2000) also reports large differences between firms in the probability a drug will be approved by the FDA, conditional on entering human clinical trials. However, this analysis does not examine whether these firm-specific effects are due to overall experience or experience in the specific therapeutic category, nor does it control for drug characteristics that may vary systematically by firm.

Henderson and Cockburn (1996) and Cockburn and Henderson (2001) use data on research inputs and outputs for 10 pharmaceutical firms to examine determinants of R&D performance at the level of the firm and research program. For drug discovery, they find evidence of returns to scale and scope at the firm level but no evidence of returns to scale at the research program level. For drug development (clinical trials), they find evidence of returns to scope but no evidence of scale economies. When firm fixed effects are included, however, the coefficient on the economies of scope variable becomes insignificant, which leaves unsettled whether firm-specific strategies or breadth of development activities explain the differential success rates.

Although these studies produce interesting results, they leave many questions unanswered. The studies by Cockburn and Henderson are based on data for the period 1961-1990, which largely predates the biotech and genomics revolution, which changed the nature of R&D and, consequently, industry structure. Their sample of 10 firms appears to consist primarily of large firms, hence is not representative of the more numerous small and medium sized firms that now dominate the industry in terms of number of firms involved in R&D, although not in terms of sales. Much of their variation is within their 10 firms

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company submits the data and files a New Drug Application (NDA) with the FDA for regulatory review and

over time rather than between firms, therefore measures of scale and scope may be contaminated by technological and other time-related changes, since most firms have grown and become more complex over time. Thus extrapolating from this sample to the larger universe of firms currently active in R&D, which includes many small firms, may be problematic.

These studies also do not examine the role of alliances in R&D productivity. As the technologies of drug R&D have changed since the 1980s, so have the role of biotech companies and of pharmaceutical-biotech alliances. The studies cited above also pre-date many of the horizontal mergers between large pharmaceutical firms that occurred in the late 1980s and 1990s, which were supposed to improve R&D productivity through economies of scale and scope. The 1990s has also witnessed the growth of contract research organizations (CROs) that specialize in conducting clinical trials. The experience of the largest CROs probably now rivals that of the large pharmaceutical companies. Since both small and large firms use CROs, it is an empirical question whether this mitigates any scale or scope effects that may previously have existed when drug development was managed in-house by pharmaceutical firms. Thus the average success rates in DiMasi's, studies and the scale and scope relationships identified by Henderson and Cockburn, may have changed considerably.

In this paper we develop more current and more detailed estimates of R&D success probabilities, by type of drug and type of firm, using data on over 900 firms for the period 1988-2000 from Adis International. Specifically, we estimate the effect on phase-specific success rates of a firm's overall experience; its experience in the relevant therapeutic category; the diversification of its experience, as measured by a Herfindahl index; and its alliances with large and small firms. We measure overall and category-specific experience as the number of compounds with which the firm was involved as an originator or a licensee during our observation period. This variable captures several dimensions of experience that may affect productivity. Within a firm, learning-by-doing may produce general skills and category-specific skills in designing and managing trials. Experienced firms may develop better

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approval.

relationships with the clinicians who conduct the trials and with regulators who evaluate them, which may allow them to run trials more efficiently and avoid errors. The total experience measure will be highly correlated with firm size and hence with other possible advantages of scale, such as spreading the fixed costs of capital equipment or information systems over a greater number of drug candidates. Further, large firms that can fund R&D from retained earnings may face a lower cost of capital than smaller firms that rely on external financing from private or public equity markets or alliances with larger firms (Mayers and Majluf, 1984). Thus, to the extent that our experience measure is correlated with size, it may capture more traditional scale effects in addition to pure experience effects.

A second and related focus of this paper is to describe the rich landscape of alliances between small and large firms, at different stages of drug development, and to examine the impact of alliances on R&D success rates. New technologies for drug discovery -- including applied microbiology, genomics, high throughput screening, combinatorial chemistry, and bioinformatics (see for example, Carr, 1998) have revolutionized the methods of drug discovery and the types of drugs that emerge. Small firms have played a key role in developing these new technologies, but most small firms ultimately try to generate products rather than rely on royalty revenues from out-licensing their technologies. These small firms often develop drug leads and then out-license these leads to large pharmaceutical firms, who then take the drug candidates through lead optimization, development and clinical trials, and ultimately regulatory approval. For example, the 20 largest pharmaceutical firms signed an average of 1.4 alliances per year with a biotech company during 1988-1990, but 5.7 such alliances per year in 1997-1998.[2] One rationale for these alliances is that the experience of large firms in drug development adds sufficient value to offset the costs of operating the alliance (Nicholson, Danzon, and McCullough, 2002). We test the hypothesis that alliances do in fact enhance success probabilities, presumably because the large licensing partner has more experience than a small originator firm. Given the maturing of the first generation biotech companies into fully integrated firms and the increasingly important role of the smaller, discovery-

[2] Recombinant Capital RDNA Database.

focused biotech companies, estimates of R&D success rates and productivity of pharmaceutical R&D must include these smaller firms and the increasingly important role of alliances.

Our data set contains information on over 1,900 compounds under development in the US by over 900 firms between 1988 and 2000. In principle, the data set includes the universe of drugs in development in the US, but in practice the data are incomplete, as discussed below. Nevertheless, this is one of the most comprehensive databases available on drugs under development in the US. We observe whether a compound successfully completes phase 1, phase 2, and phase 3 clinical trials, characteristics of the drug (i.e., therapeutic category and number of indications), the name of the company that originated the drug and the name of the companies that in-licensed the drug, if any. We use these data to calculate each firm's experience, overall and by therapeutic category. We use a logistic regression to estimate how drug and firm characteristics affect the likelihood that a drug will successfully complete each phase of clinical trials.

We find that success probabilities vary systematically across therapeutic categories and that these probabilities are negatively correlated with mean sales by category. Simple models of entry or of optimal allocation of a firm's R&D budget across drug candidates suggest that the profit- maximizing firm would be willing to accept a relatively low R&D success probability when expected sales, conditional on reaching the market, are large. Our findings are consistent with such dynamic entry.[3]

For phase 1 trials, which focus on safety and are relatively straightforward, returns to experience are statistically significant but economically small. However, for the larger and more complex late-stage trials that focus on efficacy, we find evidence of large, positive, and diminishing returns to a firm's overall experience (across all therapeutic categories). There is some evidence that a drug is more likely to complete phase 2 if developed by firms with considerable therapeutic category-specific experience and by firms whose experience is focused rather than broad (diseconomies of scope). Although a major reason

[3] Dranove and Meltzer (1994) find that important drugs, whether defined by size of potential market or therapeutic novelty, are developed faster. This is further evidence that R&D outcomes are to some extent endogenous.

given for recent horizontal mergers between large pharmaceutical firms has been the potential for economies of scale and scope in R&D, we find no evidence that scale improves productivity beyond a threshold size.

Our results confirm that alliances with large firms increase the probability of success in clinical trials for drugs originated by small firms. Thus unlike Pisano (1997), we find no evidence of a "lemons" problem in biotech outlicensing. Specifically, the positive benefit from collaboration with a more experienced partner appears to dominate any moral hazard effect that might result from the sharing of gains in alliances, and any lemons or adverse selection effects. We find no evidence that large pharmaceutical firms put less effort into in-licensed compounds than compounds that they develop internally, as the biotechnology firms sometimes allege. On the contrary, large firms have higher success rates on compounds that they in-license than on compounds that they originate in-house. This is consistent with DiMasi (2001) and Arora, Gambardella, Pommolli, and Riccaboni (2000), but not Pisano (1997).

Determinants of Pharmaceutical and Biotech R&D Productivity: Theory and Previous Literature

Henderson and Cockburn (1996) use up to 30 years of data on the inputs (research spending) and outputs (patents) of pharmaceutical research programs to test for returns to scale and scope in drug discovery/research and knowledge spillovers within and between firms. Their sample includes 10 U.S. and European pharmaceutical firms of different sizes, which collectively accounted for 25 percent of worldwide pharmaceutical research. The dependent variable is the number of important patents filed by a research program (e.g., depression, anxiety). They define overall scale as a firm's total research expenditures, scale at the research program level as research expenditures in that particular program, scope by the number of research programs in which a firm spent $500,000 per year or more on average, and the "focus" of a firm's research by a Herfindahl index of research expenditures across all research programs within a firm. For drug discovery, they find evidence of returns to scale at the firm level but not

at the research program level: a research program's patent output does not increase with program spending but does increase with the firm's total research spending (across all programs). Firms with diversified research programs also appear to file more patents, providing support for returns to scope. They also find evidence of knowledge spillovers within firms between related research programs (programs within the same therapeutic category), and between firms with the same and related programs.

Cockburn and Henderson (2001) extend their earlier work to examine scale and scope economies in the development or clinical testing phase of R&D, which follows compound discovery. Using the same data set of 10 pharmaceutical firms as in Henderson and Cockburn (1996), they measure scale as the firm's total development expenditures and scope as the number of research programs in which the firm allocates an average of at least $1 million per year. Their unit of observation is a development project that has entered human trials (phase 1), and the dependent variable is one if the project produced a new drug application to the FDA, and zero otherwise. They find evidence of returns to scope in development and returns to experience within a therapeutic category, but no evidence of overall scale economies. When firm fixed effects are included, however, the coefficient measuring economies of scope becomes statistically insignificant, which raises the possibility that firm-specific strategies, rather than breadth of development activities, explain the differential success rates. Neither of the two studies cited above examine the role of alliances in R&D productivity.

In theory, there are several reasons why firms may enter into alliances and hence why alliances may affect the observed outcome of clinical trials (see Kogut, 1988, for a summary). First, simple theory of exchange and contracting over property rights predicts that an originator firm will out-license a drug and pursue drug development with a partner if the expected benefits exceed the transactions and other costs of licensure. If co-development alliances serve to pool experience and transfer rights to firms with greater expected productivity than the originator firms, alliances should have a positive effect on success probability. The gains-from-trade effect of alliances would likely be greatest for relatively inexperienced

firms, for later stage trials that are more complex (phases 2 and 3), and in alliances with relatively experienced firms.

There is evidence that some biotech firms enter alliances to raise capital and to send a signal to the public and private capital markets that its management and science are high quality (Nicholson, Danzon and McCullough, 2002). If alliances are undertaken for this reason alone, there may be no impact on the likelihood of advancing in clinical trials.

A negative effect of alliances is also possible if there are significant moral hazard effects, since the each party's cost of effort is fully internalized whereas the returns to effort are shared with the alliance partner. The moral hazard disincentive may be more problematic on early-stage deals (preclinical and phase 1) because the originating company typically receives only about 10 percent of gross sales as a royalty. However, since this moral hazard risk is obvious, the parties to an alliance typically structure the contract and monitoring systems to deter such behavior. Potential moral hazard may be further mitigated by reputation and other positive spillover effects that accrue to small and large firms that collaborate successfully in bringing a drug to market.

A third -- not mutually exclusive -- theory of alliances is the lemons theory articulated by Pisano (1997), which posits that any potential positive gains from trade are swamped by the negative selection effect, whereby small firms out-license their least promising compounds and develop their more promising candidates independently. This is allegedly possible due to asymmetric information in the market for deals; the out-licensing firm is assumed to know more about a compound's true quality, including success probability, than the in-licensing firm. With asymmetric information, firms would have incentives to out-license their least promising compounds only. Such asymmetric information and resulting lemons effect is more likely in early-stage deals (preclinical or phase 1) than in later-stage deals signed after the phase 1 information on a drug's safety becomes publicly available. Thus, the lemons hypothesis predicts a negative effect of co-development on a drug's probability of success in clinical trials, particularly for phase 1 trials. A market for deals could still exist if the price of deals is

appropriately adjusted downward to account for this adverse selection risk faced by the in-licensing firm, and if contracts are structured to minimize selection incentives, such as by back-loading most of the out-licensing company's payments until the drug has been approved.

The empirical evidence on the impact of drug development alliances is mixed. Lerner and Tsai (2000) find that alliances formed when it is difficult for biotechnology companies to raise public and private equity assign most of the property rights to the licensing firm, and these alliances are less likely to generate an approved drug than alliances signed in periods of more favorable financing. Arora *et al.* (2000) and Nicholson, Danzon, and McCullough (2002) conclude that drugs developed in alliances are more likely to advance in clinical trials than drugs developed by the originating company, while Pisano (1997) comes to the opposite conclusion using a smaller and older data set. None of the above studies examine whether the performance of alliances varies according to the experience of the originating and licensing companies.

Hypotheses

This paper tests the following principal hypotheses with respect to the effect of firm experience and alliances on R&D productivity. These are elaborated below:

1. If experience increases R&D productivity, we expect success probabilities to be positively related to firm experience, as measured by the number of compounds with which the firm was involved as an originator or licensee during our observation period. We test for differences between total and category-specific experience. These variables may reflect accumulated technical skills, learning-by-doing in the management of trials, formation of relationships with clinicians and/or regulators and – particularly for total experience – scale economies such as spreading the fixed costs of information systems and capital equipment. We test for non-linear effects, since diminishing returns to such economies of scale seem plausible, due to the increasing management challenges of operating very large research establishments, including motivating scientists. We also test for experience-based economies of scope,

measured by a Herfindahl index of the dispersion of the firm's experience across different therapeutic categories.

2. If alliances on balance increase R&D productivity (that is, any negative lemons and/or moral hazard effects are dominated by positive gains from collaboration), success probabilities are expected to be higher for compounds that are co-developed. We expect these gains from trade to be greater for alliances between an inexperienced firm and a more experienced firm than for alliances between two relatively experienced firms. Productivity gains are also expected to be greater for the more complex phase 2 and phase 3 trials than for simple phase 1 trials.

Data

Our principal data source is the R&D Insight database from Adis International. Adis has collected information on 1,910 compounds that were under development by pharmaceutical and biotech firms in the United States between 1988 and 2000, with most of the observations occurring after 1994. The dataset contains information on characteristics of the compound, including the therapeutic category or categories (e.g., cardiovascular, central nervous system) and the indication(s) the drug is intended to treat (e.g., colon cancer, anxiety). The 13 different therapeutic categories are based on the World Health Organization's (WHO) typology. Sample means and standard deviations are presented in Table 1, separately by development phase.

Our unit of analysis is a specific indication for which a drug is being developed, rather than a drug or development project. Since the FDA requires clinical trial evidence to establish efficacy for each indication for which a drug is approved, separate trials are usually required for each indication. Thus an indication represents the most disaggregated unit of R&D output. A further advantage of analyzing performance separately by indication is that alliances between companies sometimes cover some but not all of a compound's indications. If a drug is successful for one indication, a firm may be more likely to initiate clinical trials for additional indications. We therefore include in our regression analysis the

number of indications for which a drug is or has been tested, as a proxy for this unmeasured quality of the compound. In our database, phase 1 drugs were developed for 3.4 separate indications, on average, phase 2 drugs for 3.1 indications, and phase 3 drugs for 3.0 indications. In the Adis database, each indication for which a compound is being developed is coded as being in the same therapeutic category. We report robust standard errors to control for correlation of unobserved characteristics across indications for a given compound.

Using indication as the unit of observation differentiates our analysis from Cockburn and Henderson (2001) and Henderson and Cockburn (1996), who analyze output at the level of an entire development project or research program, which may consist of multiple compounds, each for multiple indications. Hereafter we use "compound" to refer to the molecule and drug, and indication to refer to a condition the compound is intended to treat.

We measure overall experience (Total Experience) at the firm level by the total number of compounds a firm was involved with, either as an originator or a licensee, during our 1988 to 2000 sample period. This experience measure includes compounds in both preclinical and clinical stages because we believe that preclinical experience can potentially inform the conduct of the three stages of human clinical trials that are the focus of our analysis. In some specifications we classify firms as small, medium, or large, in place of the continuous Total Experience measure. A small firm is defined as one with three or fewer compounds in development during the sample period, a medium-sized firm as one with between four and 24 compounds in development, and a large firm as one with 25 or more compounds in development. There are 961 firms in our sample, of which 776 are small, 163 medium-sized, and 22 are large by these criteria. Some specifications include fixed effects for the 22 large firms. Controlling for experience and therapeutic class of the compound, these firm fixed effects test for firm-specific drug development proficiencies.

In the Adis database firm names are updated to reflect merger and acquisition information. Thus our measures of industry structure and firm-specific experience reflect the experience at the end of our

sample period (2000), not the contemporaneous experience. A drug that was originated in 1992 by Upjohn, for example, will be credited to Pharmacia, reflecting the 1996 merger between Pharmacia and Upjohn. Although this could introduce some measurement error in our measure of firm experience, the effect should be small because 83 percent of the observations in our analysis are from the 1996-2000 period. Since many of the large mergers occurred prior to 1996, the current company names are appropriate for the majority of our observations. We note below where the estimated effects of experience may be biased for the largest firms, since measurement error in experience is likely to be greatest for large firms formed through mergers.

In order to examine whether therapeutic category experience matters, conditional on a firm's overall experience, we define therapeutic category-specific experience (Therapeutic Experience) as the number of compounds a firm has originated or in-licensed in the therapeutic category of interest. If multiple therapeutic categories are reported for a given compound, the firm's maximum experience across these therapeutic categories is assigned for that compound. Therapeutic and Total Experience are highly correlated (correlation of 0.78), which may make it difficult to precisely estimate each effect separately.

We use a Herfindhal-Hirschman index (HHI) to measure experience-based economies of scope (Scope). Specifically, a firm's Scope measure is the proportion of its total number of compounds accounted for by each therapeutic category, squared and summed across all therapeutic categories in which the firm is active. Thus small firms that focus their activity in a small number of therapeutic categories have an HHI measure close to one. When two or more companies are jointly developing a compound, we assign the experience and scope measures of the more experienced firm to the compound, assuming that the larger firm is likely to take on greater responsibility in managing the clinical trials (Lerner and Merges, 1998). Our experience and scope measures are on based on numbers and distributions of compounds, whereas Cockburn and Henderson (2001) measure scale as the firm's total R&D expenditures or the R&D expenditures in a particular development project, and scope as the number of development projects with average annual R&D expenditures in excess of $1 million. Since we do not

have data on expenditures, we unfortunately cannot compare the predictive performance of these two approaches to measuring scale and scope.

In order to test for the effects of alliances, we create an indicator variable (Alliance) that equals one if two or more firms were involved in the development trials for that indication.[4] This variable is phase-specific and includes only alliances that were formed prior to the conclusion of the development phase of interest, in order to avoid the potential for endogeneity bias that could result if more successful projects are more likely to be subject of deals.[5] We interact the alliance indicator variable with the experience of the originator firm and the licensee to test whether the effect of alliances varies by experience of either party.

Estimating the effects of alliances on R&D success requires caution because alliances are formed by choice. In a well-functioning market for alliances, firms would partner and collaborate on products where the gains from trade are likely to be highest and skill sets are most complementary. On the other hand, if information is asymmetric, small firms may take advantage of their superior knowledge to out-license their least promising candidates (Pisano, 1997). If either positive or negative sorting occurs based on unobserved (to the econometrician) drug characteristics, then our estimate of the effect of an alliance on the likelihood a drug will advance in clinical trials may not be the true causal effect of an alliance. We control for this to the extent possible by including the therapeutic category of the indication in question. Nevertheless, our results should be interpreted as estimating the effect of an alliance, conditional on its occurrence prior to the phase under study.

Firms may differ in the quality of their drug candidates and in how rigorously they evaluate the likelihood each drug will succeed in clinical trials prior to beginning the first clinical trial (phase 1). On

[4] The alliance variable is set equal to one if the database lists a licensee or two or more originators. When the database lists two or more originators but no licensee, we assume the company with the smallest number of drugs in development during our sample period is the originator and the larger firm is the licensee, because it is much more common for small firms to outlicense to large firms than vice versa. When more than one licensee is listed, we assign licensee status to the largest firm.

[5] We use data from three databases, Adis' R&D Insights, Windhover and Pharmaprojects, to determine the date of deals.

the one hand, it is often argued that small firms that are under pressure to provide results in order to raise external funds are more likely to take a compound into clinical trials than larger firms that typically use retained earnings to fund their R&D. On the other hand, it is also argued that researchers in large firms act as champions for their own compounds and that this may lead to less rigorous and/or less objective scrutiny than the scrutiny of external markets that is applied to the compounds of small firms that rely on external funding. In order to measure the unobserved quality of a compound due to a firm's capabilities and/or its stringency in selecting compounds to take into clinical trials, we calculate for each firm a variable called Screening Ratio, defined as the number of compounds a firm takes into clinical trials divided by the sum of the compounds in clinical trials plus preclinical compounds that do not enter trials.[6] The Screening Ratio can range from zero to one. Firms that set higher standards in selecting the compounds that they take into clinical trials would be expected to have higher success rates in the clinical trials, assuming no systematic differences across firms in the quality of compounds evaluated in the preclinical phase. In this case Screening Ratio would be inversely related to success probability, under the hypothesis that a low screening ratio implies relatively strict review criteria prior to human trials, hence high unobserved "quality". It is also possible that firms don't vary systematically in the expected success probability they require to take a compound into clinical trials. In that case, a low Screening Ratio would indicate that a firm's preclinical drugs are of poor quality, but this would be uncorrelated with the success probability of drugs that are taken into clinical trials.

Methodology

We perform a series of logistic regressions to analyze the determinants of R&D productivity, where the dependent variable is one if a compound successfully completes a phase for a particular indication, conditional on starting that phase, and zero if the trial for that indication is discontinued. Our

[6] Drugs in the preclinical stage after 1998 are not included when calculating the screening ratio variable because we don't observe these drugs for a long enough time to conclude they will never begin clinical trials.

sample consists of 2057 observations for phase 1, 1275 observations for phase 2, and 861 observations for phase 3.[7]

The data suffer from both left- and right-hand censoring. Left-hand censoring occurs, for example, if we observe that a phase 2 trial was initiated for a particular indication but we have no information on the phase 1 trial. In this situation we include the observation in the phase 2 regression (and the phase 3 regression if the phase 2 trial is successful), but exclude it from the phase 1 regression. If we instead imputed a successful phase 1 trial and included this observation in the phase 1 regression, our advancement probabilities would likely be biased upward due to survival bias. It is reasonable to assume that the Adis database tracks a larger percentage of the universe of later-stage trials than early-stage trials because late-stage trials are more likely to be discussed at public conferences and by investment analysts. If this is the case, then drugs that are discontinued in the preclinical or phase 1 stage are less likely to be included in the database than drugs that complete phase 1. By including a drug only when we observe that it begins a development stage, we mitigate the potential survival bias that could result from such incomplete reporting. Since the FDA requires the filing of an Investigational New Drug (IND) application before a drug can enter human clinical trials, the data should be reasonably complete for drugs that make it into human clinical trials.

Right-hand censoring occurs when we do not observe whether an indication completed a phase successfully or was discontinued. Rather than eliminating these observations from the regressions, we assume that an indication failed if it remained in a phase, without any further reported events, for more than a threshold value, defined as the maximum number of years observed for completion of each phase in the non-censored sample. These thresholds are 5 years for phases 1 and 3, and 6 years for phase 2. For example, if an indication entered phase 1 or 3 before 1996 and no further action is reported by 2000, we assume that it failed and code the dependent variable as a zero. Indications that entered those phases in

[7] The data on dates of various events related to a drug's development -- including when a company initiates, completes or terminates a development phase for an indication, or receives FDA approval– are incomplete, hence the available sample size was too small to examine the time to completion using a hazard model.

1996 or later and contain no additional information are excluded from our regression analysis. We apply the same procedure to indications in phase 2 using 1995 as the threshold.

Results

We begin by examining the extent to which development success rates vary across therapeutic categories. In Table 2 we report coefficient estimates from separate logit regressions for phase 1, phase 2, and phase 3, where the only regressors are therapeutic category indicator variables. Since the therapeutic categories are not mutually exclusive -- a compound can target multiple therapeutic categories -- all 13 therapeutic category indicators are included in the regressions. Coefficients are therefore interpreted as deviations from the overall average across all therapeutic categories.

The predicated probability that an indication will advance differs from the overall average for three of the 13 therapeutic categories in phase 1, six of the therapeutic categories in phase 2, and seven of the therapeutic categories in phase 3. There is considerable variation across therapeutic categories in the likelihood of succeeding. For example, the predicted probability that an indication will be approved by the FDA, conditional on starting a phase 3 trial, ranges from 0.53 for central nervous system drugs to 0.89 for hormone preparations. The fourth column of Table 2 reports the predicted probability that the FDA will approve an indication, conditional on starting phase 1. This value is obtained by multiplying the three phase-specific predicted probabilities of success for each therapeutic category from the regression estimates. Drugs for respiratory indications have the lowest predicted probability of being approved (0.30) whereas hormone preparations have the highest predicted probability (0.78).

Our indication-specific predicted probabilities of approval, conditional on entering human trials, are somewhat higher than the 0.20 probability across all therapeutic categories that DiMasi (2001) estimates using the Tufts CSDD data. This discrepancy probably results because our unit of observation is a specific indication or condition, whereas DiMasi's unit of observation is the first indication for a new chemical entity (NCE). As discussed earlier, if companies are more likely to target multiple indications

for those compounds that have either already been approved or have a relatively high probability of being approved, then overall success probabilities will be higher for our measure based on all indications than for the first indication of a new compound. In our regression analysis below we include the number of indications a drug is targeting. The predicted sign of this variable is positive if the number of indications is correlated with the unobserved "quality" of a compound. The coefficient is expected to be larger in phase 1 than in phase 2 or phase 3 because the safety properties that are established in phase 1 are likely to be highly correlated across multiple indications for a compound, whereas efficacy (the objective of phase 2 and phase 3) is less likely to be correlated across indications.

If the pharmaceutical industry is subject to dynamic competition with few barriers to entry, we would expect firms to invest in R&D until the expected return is equalized across therapeutic categories and is equal to the risk adjusted cost of capital. The significant and large differences in success probabilities across therapeutic categories in Table 2 might seem inconsistent with this model of competitive entry unless there are offsetting differences across categories in costs of clinical trials or in expected revenues, conditional on reaching the market. In Figure 1 we plot the predicted probability that a drug will be approved in each therapeutic category, conditional on entering clinical trials (from column 4 of Table 2), versus the market size of that therapeutic category, as measured by 1991 worldwide sales. Sales in 1991 are a reasonable proxy for expected sales at the time compounds entered preclinical activity, since most of the compounds in our sample were in discovery testing in the early 1990s. In Figure 1 the correlation between the probability that a drug will reach the market and sales in the therapeutic category is –0.50. Indications targeting relatively large categories (e.g., respiratory therapy, central nervous system, alimentary, and cardiovascular) have relatively low predicted success probabilities. This evidence, that firms appear to be willing to develop drugs with a lower probability of success in therapeutic categories with greater sales potential, is consistent with the hypothesis of dynamic competition. Firms also appear to be willing to invest more to develop drugs with relatively large sales potential. The correlation between average R&D spending per development project by therapeutic

category, reported in Cockburn and Henderson (2001), and 1991 worldwide sales by therapeutic category is 0.32. Competition may, therefore, eliminate expected rents across categories on both the intensive margin (willingness to spend more per drug program) and on the extensive margin (willingness to take on riskier conditions/drugs).

The Prevalence and Pattern of Development Alliances

Development alliances are quite common, and occur for the majority of compounds by the time they reach phase 2 and 3. In Table 3 we report the number and percentage of indications that are out-licensed, by experience of the originator, experience of the licensee, and development phase. Forty-nine percent of the indications in phase 1 were developed in an alliance, and large firms were almost as likely as small and medium-sized firms to form an alliance. There does not appear to be a strong pattern regarding the size of the originator and licensee in the phase 1 alliances; small firms often form alliances with other small firms (112 indications in panel A of Table 3), and large firms sometimes form alliances with small firms (84 indications in panel A of Table 3).

For phases 2 and 3, a larger percentage of indications are co-developed and a clearer pattern emerges of medium and larger firms being the licensees. Fifty-five and 62 percent of phase 2 and phase 3 indications, respectively, are co-developed. In phase 3, large firms in-license almost as many indications as small and medium firms combined, even though there are only 22 large firms in the data set (out of 961). These findings are consistent with conventional wisdom that small firms often have the skills and resources necessary to do the relatively small phase 1 trials, but are more likely to seek a large pharmaceutical partner for the larger, more complex and more costly phase 3 trials. The evidence below on returns-to-experience confirms that these returns are relatively large for late-stage trials.

As shown in Table 3, large firms out-license a smaller percentage of indications than small and medium-sized firms, and this difference is greater for phase 3 compounds than for earlier phase compounds. Large firms are more likely to out-license to other large or medium size firms than to small

firms. The theories of alliances we described previously cannot explain why large firms would ever out-license, since they presumably have greater experience and lower financing costs than small- and medium-sized firms. There are several possible reasons why large firms engage in a considerable amount of out-licensing. First, due to the stochastic nature of drug R&D, a large firm may find itself with more potential compounds ready for development than can be accommodated by its in-house personnel. The firm may choose to handle this temporary excess by out-licensing. Second, large companies typically retain for in-house development only those compounds that exceed some minimum threshold of expected sales. If their discovery efforts produce compounds with expected sales below this threshold, they may choose to out-license these compounds to smaller companies that have lower expected sales thresholds. Third, even a large firm may out-license compounds with very large market potential in order to share the marketing expense and/or diversify its risk on the very large marketing investment required.

The first and second of these hypotheses might weakly predict that large firms would be more likely to out-license their compounds that have a lower probability of success. The third motive -- risk and cost sharing on large products -- might predict higher success probability for compounds that are out-licensed by large firms. Medium-sized firms presumably experience a blend of the factors that affect small and large firms, depending on their experience, on the stochastic shocks that affect their balance between resources/capacity and drugs entering development, and on their underlying strategies. The medium-size category includes firms that pursue very different business models and strategies, including: mature biotech firms that are fully integrated and have strong internal R&D as well as marketing capabilities (e.g., Amgen or Biogen); "specialty" companies that do not conduct discovery research but in-license niche products that are targeted at small markets that may not be of interest to large firms (e.g., Forest Laboratories); and some fully integrated foreign firms (e.g., Takeda and Celltech). We discuss the effect of alliances on success probabilities below.

Experience-based Economies of Scale and Scope

We first examine whether there is evidence of experience-based economies of scale and scope in drug development. We include two measures of experience: Total Experience is a count of the total number of compounds the firm developed, either as an originator or as a licensee, during our 1988-2000 sample period, and Therapeutic Experience is the number of compounds the firm developed during our sample period in the same therapeutic category as the drug being evaluated. Experience-based Scope is measured using a Herfindahl index (HHI) of the squared shares of compounds in each therapeutic category in which the firm is active. For each phase, the first logit specification reported in Table 4 (columns 1,3, and 5) includes Total Experience, its squared term, Scope, and Therapeutic Experience, but not Screening Ratio (the percentage of a firm's preclinical compounds that enter phase 1). The second logit regression for each Phase (columns 2, 4, and 6) includes the Screening Ratio. The experience measures might be subject to endogeneity bias if firms whose drugs are more likely to advance have more drugs under development, for example, because these firms are more attractive as licensing partners. However, since our experience measures include all compounds with which a firm was associated in both preclinical and clinical trials, regardless of whether the compound failed or succeeded, such bias should be minor.

The regressions in Table 4 indicate substantial returns to Total Experience for the more advanced clinical trials (phase 2 and phase 3) but not for phase 1. In phase 1, there appears to be a convex relationship between a firm's total experience and the probability an indication will advance to phase 2 (column 1 and column 2). As depicted in Figure 2, the predicted probability that an indication will advance if developed by a firm that has originated a single drug is 0.93. This predicted probability declines gradually with experience until it reaches a minimum of 0.88 for firms that have developed 120 drugs, and then increases slightly thereafter. Therefore, the magnitude of the effect of experience on the predicted probability an indication will complete phase 1 is small. Controlling for Total Experience, category-specific Therapeutic Experience is not significant.

In phase 2, by contrast, there is a concave effect of the originating firm's Total Experience on the likelihood of completing a clinical trial, and the magnitude of the impact is larger than in phase 1. The coefficient on the linear Total Experience variable is significant and positive while the coefficient on the quadratic term is significant and negative. The predicted probability of a phase 2 success for an indication originated by a one-drug firm is 0.63 (see Figure 2). This predicted probability of a phase 2 success increases with the experience of the originator until it reaches a maximum of 0.80 with an experience level of 100 drugs, and then decreases thereafter.[8] Therapeutic Experience is positive and significant in phase 2 when we include the Screening Ratio variable to control for unobserved characteristics of a compound that may affect its likelihood of succeeding in clinical trials (column 4). The predicted probability that an indication will complete phase 2 increases by about 0.3 percentage points (on a base of 78.0) for each additional compound the firm has developed in that therapeutic category.

For phase 3 (columns 5 and 6 of Table 4), Total Experience and its squared term are jointly significant, and there appears to be a slightly concave effect of experience, as in phase 2. The predicted probability that an indication will complete phase 3, conditional on beginning that phase, if the originating firm developed 10 drugs during our sample period is 0.40, versus 0.68 for a firm that developed 150 drugs. Thus Total Experience appears to become more important in each development stage. By contrast, there is no evidence of returns to Therapeutic Experience in Phase 3.

Our findings, that a firm's experience in R&D does not substantially affect the likelihood that an indication will complete phase 1 but has a considerable effect in phase 2 and phase 3, are consistent with conventional wisdom: small firms are able to perform the relatively small and simple phase 1 trials for safety whereas experience matters for the larger and more complex phase 2 and 3 trials, which require perfecting the dosage and establishing statistical evidence of efficacy in large patient samples. Firms that have performed more phase 2 and phase 3 trials appear to be more successful at subsequent phase 2 and

phase 3 trials. Thus, success in a late-stage trial provides a more robust measure of the quality of the compound and/or the development expertise of a firm than a phase 1 success. The decision to enter a phase 3 trial, for example, implies not only that the phase 2 trial produced good evidence of safety and preliminary evidence of efficacy, but also that the economic evaluation of the drug is sufficient to warrant making the much larger investment in phase 3 trials. Thus, success in phase 2 is a more important measure of clinical potential than success in phase 1, and success in phase 2 also implies significant economic potential.

The finding that experience has a positive effect on the probability that an indication will complete phase 2 and phase 3 trials is consistent with the evidence from alliances in Table 3, that smaller firms are more likely to seek out partners for phase 2 and 3 trials than for phase 1. This is confirmed by the estimated effect of these alliances in Table 4. Co-developed indications are no more likely to complete Phase 1 than drugs that are developed independently by the originating company (column 1 of Table 4). However, indications developed in an alliance are significantly more likely to complete phases 2 and 3 than indications developed independently, and the marginal impact of an alliance is higher for phase 3 than phase 2. In phase 2, the probability a co-developed indication will advance is 6.8 percentage points higher than an indication that is developed by its originating company (0.830 versus 0.780) for a firm and indication with the sample mean characteristics. For phase 3, co-developed indications have an 11-percentage point higher (0.681 versus 0.569) predicted probability of advancing. Almost two thirds (62.1 percent from Table 3) of indications are under co-development by phase 3, and the majority of licensees for phase 3 are medium or large firms.

Controlling for Total and category-specific Therapeutic Experience, we find no evidence of returns to scope or diversity, as measured by the HHI of a firm's experience across therapeutic categories, for phase 1 or phase 3. When we control for unobserved drug characteristics with Screening Ratio, we do find evidence of negative returns to experience-based scope in phase 2. In other words, firms that focus

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[8] Since there are only two firms in our sample that developed more than 160 drugs between 1988-2000, we cap

their research efforts on a smaller number of therapeutic categories, and thus have a relatively high HHI measure, are more likely to have their indications complete phase 2. A one standard deviation increase in Scope is associated with a 3.8 percentage point increase in the likelihood that an indication will complete a phase 2 trial. Cockburn and Henderson (2001) find significant evidence of economies of scope but no evidence of economies of scale in drug development over the entire three development phases. These two sets of findings are not necessarily inconsistent because they pertain to different samples, different time periods and different measures of scale, scope and success. Cockburn and Henderson (2001) use a sample of 10 firms for 1960-1990, their measures of scale and scope are dollar outlays, their measure of success is the probability a drug was approved by the FDA conditional on starting phase 1, and they do not control for alliances. Our sample of almost 1,000 firms includes many more observations on firms in the small- and medium-size range where returns to experience are likely to be most important.

In Table 4, the number of conditions for which a drug is being developed is significantly positive, consistent with the hypothesis that multiple indications are more likely to be pursued for drugs that have already succeeded or are likely to succeed. This effect is greater for phase 1 than for phases 2 and 3, as expected if the probability of showing efficacy (phases 2 and 3) is less strongly correlated across indications for a given molecule than the probability of showing safety (phase 1). The coefficient on Screening Ratio is positive and significant for phase 2 and phase 3; firms that initiate phase 1 trials for relatively large proportion of their preclinical drugs are more likely to experience phase 2 and phase 3 successes. This suggests that this variable is measuring unobserved characteristics of a compound rather than different stringency levels of firms' internal review processes.

The next question we explore is whether large pharmaceutical firms differ in their productivity, conditional on their total experience and the scope of their development activity. In Table 5 we report coefficient estimates of logit regressions that include a vector of firm fixed effects for the 22 firms with

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experience in Figure 2 at 160.

25 or more drugs under development during the sample period. The reference group for the firm coefficients is thus firms with 24 or fewer drugs under development during the period. We interact Total Experience and the quadratic experience term with an indicator variable if the firm developed 25 drugs or more to allow experience to have a different effect for small versus large firms.[9]

There is very little difference across firms in performance in phase 1. Adding firm fixed effects does little to improve the fit of the phase 1 regression (column 1 of Table 5 versus column 1 of Table 4). Only one of the 22 firm coefficients is significantly different from zero and the firm effects are not jointly significant. The experience coefficients for relatively small firms are insignificant when firm fixed effects are included for the largest firms.

The firm fixed effects in phase 2 are jointly significant (column 2 of Table 5) and 13 of the 22 firm coefficients are significantly different from zero at the 10-percent level. The predicted probability that an indication will complete phase 2 varies by 11 percentage points among the 13 firms that have significant firm fixed effects. The coefficient on the linear Total Experience term is negative, suggesting that there are negative returns to experience among small and medium-sized firms (firms that have developed fewer than 25 drugs during our sample period). By contrast, returns to experience in phase 2 are positive when the entire range of firms is used to identify the relationship.

Firm fixed effects are also significant in phase 3. The pseudo R^2 of the logit regression increases substantially (from 0.13 in column 5 of Table 4 to 0.20 in column 3 of Table 5) when the firm fixed effects are included in the phase 3 regression. The firm fixed effects are jointly significant and five of the 22 firm indicators are significantly different from zero. The predicted probability that an indication will complete a phase 3 trial spans a much wider range than for phase 2, from 0.71 to 0.94 among the five firms with significant coefficients. As in phase 1, the Total Experience measures become insignificant once we control for firm fixed effects, which suggests there are no systematic returns to experience

[9] The specifications in Table 5 omit Screening Ratio because it is highly correlated with some of the firm-specific coefficients.

among the sample of firms with medium and low experience. Only a few of the other coefficients change substantially when we include firm effects: the Scope variable is no longer significant in phase 2 and the Alliance variable is about 20 percent smaller in phase 3.

Effect of Alliances

We next explore in more detail whether indications that are co-developed in alliances are more or less likely to advance in clinical trials than indications developed in-house by the originator firm, and whether the impact of an alliance varies with the experience of the originator and licensee firms. In Table 6, the first specification for phases 1, 2 and 3 trials (columns 1, 3 and 5 respectively) include indicator variables for indications originated by small and medium-sized firms (large firms are the omitted group).[10] Three separate indicator variables are included that equal one if a small, medium, or large firm forms an alliance on an indication. The second specification (columns 2, 4 and 6) tests whether the outcome of an alliance depends on the size/experience of the licensee as well as the size/experience of the originator, by interacting the alliance indicator variables for small and medium-sized firms with indicators for small and large licensees (medium-sized licensees are the omitted group). All equations also include indicators for an indication's therapeutic category and the number of conditions for which the drug is in trials.

For phase 1 (column 1), the estimated effects of co-development are significantly negative for small firms but insignificant for medium-sized firms. For small firms, the coefficient on co-development of –0.546 suggests that the compounds small firms out-license are significantly less likely to complete Phase 1 than compounds they develop on their own. This result may support the hypothesis that asymmetric information allows small companies to dump their "lemons" on unsuspecting partners (Pisano, 1997). Alternatively, small firms may invest less time in a partnership due to moral hazard.

[10] We define small firms, or firms with relatively little experience, as those that developed three or fewer compounds in our data set, medium-sized firms between four and 24 compounds, and large firms 25 or more compounds.

However, controlling for the experience of the licensee (column 2) shows that this potential lemons or moral hazard problem does not apply to alliances between small originators and large firms. The predicted effect of an alliance between a small originator and a large licensee is the sum of the –0.886 and 0.885 coefficients, which is not statistically different from zero. One possible explanation for this result is that large firms have sufficient experience in evaluating and managing deals to prevent a small firm from dumping its low-quality compounds or shirking in alliances with large firms. Alternatively, it may be the case that the value of a licensing partner is positive in phase 1 only if the partner is large. These data do not permit us to distinguish between the selection bias and gains-from-trade explanations of the difference between co-development with large medium licensees. The net effect seems to be that the drugs that small firms out-license to large firms do as well as those the small firms develop on their own, but the drugs they out-license to medium-sized firms are less likely to complete phase 1 than the drugs the small firms develop on their own. The predicted probability that an indication originated by a small firm will complete phase 1 if they form an alliance with a large firm is nine percentage points higher than if they form an alliance with a medium-sized firm (0.924 versus 0.834). For compounds originated by large firms, outlicensing has no significant effect on phase 1 success rates.

In phase 2 (column 3 of Table 6), indications that small firms out-license are more likely to complete phase 2 than indications they develop on their own, in contrast to the phase 1 result, with no significant difference by size of licensee. This is consistent with the hypothesis that larger, more experienced firms have an advantage in running later-stage trials relative to smaller firms. Medium-size originators gain from an alliance for phase 2 trials and this effect is greatest if the alliance is with a large firm. This is further evidence that alliances add greatest value when the licensee is larger than the licensor. For an indication from a medium-sized originator, the predicted probability of completing phase 2 is 25 percentage points higher if the firm forms an alliance with a large firm than if the indication is developed in an alliance of two medium-sized firms (0.852 versus 0.604). These results generally support the view that large, experienced firms are either competent at picking good drugs to in-license and/or

competent at managing the alliances once they are formed and that these positive effects of alliances dominate any moral hazard effects.

For phase 3 (columns 5 and 6), indications that medium and large firms originate and develop in an alliance are more likely to complete phase 3 than indications these firms develop independently. When we add originator-licensee experience interactions, alliances that medium-sized companies form with medium and large firms appear to outperform alliances they form with small companies, but this effect is significant at only the 12 percent level. The perhaps surprising finding of no significant effects of alliances in phase 3 for indications originated by small firms, in contrast to the significant positive effects in phase 2, may reflect the relatively small sample of indications that are originated by small firms and enter phase 3 (178 enter phase 3 versus 322 that enter phase 2 and 635 that enter phase 1) and the small percentage (only 30 percent) of these that the small companies are developing on their own. This small sample makes the coefficient estimate imprecise. It may also be subject to biased selection, if small firms choose to undertake phase 3 trials without a partner only on those drugs for which they either have the necessary experience or are most confident in the quality of the compound.

The results for other variables are consistent with previous findings. For phase 1 and phase 2, the Screening Ratio is positive, implying that firms taking a high percentage of their pre-clinical compounds into human trials also have high success rates in early trials, but with no significant difference in phase 3 trials. This confirms previous evidence that Screening Ratio measures the unobserved quality of a firm's compounds, rather than the stringency of its selection criteria.

Conclusions

We examine whether success in biotech and pharmaceutical R&D varies according to the category of the drug, the experience of the originator firm, whether the drug is developed in an alliance, and the experience of the licensee. Our database reflects the experience of over 900 firms between 1988 and 2000, including many small and inexperienced firms as well as the large multinational companies.

We find that success probabilities differ substantially across therapeutic categories. The significant negative correlation between success probability and potential sales in a therapeutic category is consistent with a model of dynamic, competitive entry. That is, firms appear to be willing to undertake projects with lower probabilities of success in categories where the expected sales, if successful, are relatively large.

Experience, measured by the number of compounds with which the firm was involved, does not appear to matter for phase 1 trials, which are small and relatively simple. However, for the larger and more complex phase 2 trials, there are positive returns to total experience, up to a threshold; for phase 3 the results are qualitatively similar to phase 2 but are less precisely estimated. There is also evidence of returns to category-specific experience and returns to scope or breadth of experience in multiple therapeutic categories. However, these returns to scale and scope are not robust to including firm fixed effects for the largest firms, which are jointly significant.

Products developed in an alliance tend to have a higher probability of success, at least for the more complex phase 2 and phase 3 trials, particularly if the licensee is a large firm. Thus, the evidence on effects of alliances tends to confirm the direct evidence from the economies of experience measures; experience increases the probability of success for late-stage trials, whereas it is not necessary for the simpler, phase 1 trials. These productivity-enhancing effects of alliances with large firms dominate any lemons or moral hazard effects. Overall, these results suggest that the market for pharmaceutical R&D is functioning reasonably well, with extensive entry by small firms and effective use of alliances, as a source of both funding and expertise for small firms, and a source of products for large firms.

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Table 1: Sample Means and Standard Deviations

	Phase 1	**Phase 2**	**Phase 3**
Observations (indications)	2057	1275	861
Therapeutic categories:			
Alimentary tract and metabolism products	0.145	0.156	0.150
Antithrombotic agents	0.073	0.085	0.081
Cardiovascular system	0.135	0.150	0.159
Antipsoriatics	0.116	0.120	0.115
Urologics and contraceptives	0.058	0.076	0.114
Hypothalamic hormones and analogues	0.009	0.016	0.029
Antivirals and antibacterials	0.175	0.185	0.223
Cytotoxic antibiotics and related substances	0.518	0.408	0.280
Antiinflammatory and antirheumatic products	0.135	0.149	0.166
Nervous system drugs	0.164	0.202	0.178
Agents against amoebiasis and other protozoal diseases	0.022	0.019	0.017
Respiratory system products	0.098	0.104	0.070
Carbonic anhydrase inhibitors	0.040	0.048	0.056
Average number of indications/compound	3.4	3.1	3.0
	(2.8)	(2.5)	(2.2)
Firm's total number of drugs in development (Total Experience)	54.0	68.1	80.1
	(57.6)	(59.5)	(59.5)
Firm's category-specific number of drugs (Therapeutic Experience)	18.1	20.3	22.1
	(17.2)	(17.0)	(17.1)
Scope of firm's R&D (HHI index across therapeutic categories)	0.277	0.233	0.205
	(0.232)	(0.197)	(0.169)
Screening ratio (percentage of pre-clinical drugs that begin Phase 1)	0.616	0.610	0.608
	(0.258)	(0.228)	(0.209)

Note: Standard deviations are in parentheses below each continuous variable.

Table 2: Logit Coefficient Estimates of Therapeutic Category Indicators

	Phase 1	**Phase 2**	**Phase 3**	**Predicted probability an indication is approved conditional on starting Phase**
Constant	1.612**	1.1875**	1.017**	
	(0.1449)	(0.1253)	(0.1488)	
A: Antithrombotic	0.0443	0.1939	-0.3173	0.448
	(0.2155)	(0.1888)	(0.2113)	
B: Blood	0.0426	0.1796	-0.7748**	0.375
	(0.2683)	(0.2353)	(0.2768)	
C: Cardiovascular	0.0476	-0.4077**	-0.7445**	0.327
	(0.2187)	(0.1807)	(0.2078)	
D: Antipsoriatics	0.4472	0.0732	0.126	0.524
	(0.2946)	(0.2149)	(0.2483)	
G: Urologics and	1.3509**	1.0509**	0.6004**	0.717
Contraceptives	(0.5189)	(0.3356)	(0.2624)	
H: Hormonal preparations	0.8549	1.8262*	1.0982*	0.784
	(1.0432)	(1.0343)	(0.5784)	
J: Antivirals	-0.2038	0.0911	-0.0933	0.450
	(0.1826)	(0.1744)	(0.1988)	
L: Cytotoxics	0.4563**	-0.6125**	-0.7877**	0.316
	(0.1542)	(0.1389)	(0.1748)	
M: Antiinflammatory	0.326	0.2704	0.1374	0.539
	(0.263)	(0.1997)	(0.2108)	
N: Nervous System	0.0432	-0.0322	-0.8987**	0.338
	(0.1972)	(0.172)	(0.2015)	
P: Parasitology	-0.0644	0.5817	0.019	0.520
	(0.4615)	(0.5273)	(0.5861)	
R: Respiratory system	0.6748**	-0.9102**	-0.7196**	0.296
	(0.3028)	(0.2011)	(0.299)	
S: Carbonic anhydrase	0.8321	0.825**	0.3555	0.648
	(0.5229)	(0.3716)	(0.3505)	

Note: robust standard errors are in parentheses.

Table 3: Alliance Activity by Development Phase and Experience of Originator and Licensee

Exper. of Originator	Total Observations	Observations in Alliances	Percentage in Alliances	Experience of Licensee Firm		
				Small	Medium	Large
Phase 1						
Small	635	314	49.4%	112	121	81
Medium	673	357	53.0%	36	144	177
Large	749	345	46.1%	84	189	72
Total	2057	1016	49.4%	232	454	330
Phase 2						
Small	322	202	62.7%	50	82	70
Medium	400	241	60.3%	29	74	138
Large	553	254	45.9%	48	110	96
Total	1275	697	54.7%	127	266	304
Phase 3						
Small	178	124	69.7%	24	50	50
Medium	267	192	71.9%	20	52	120
Large	416	219	52.6%	30	97	92
Total	861	535	62.1%	74	199	262

Table 4: Experience-based Economies of Scale and Scope in Pharmaceutical/Biotech Drug Development

	Phase 1		**Phase 2**		**Phase 3**	
	(1)	(2)	(3)	(4)	(5)	(6)
Total Experience	-0.0106*	-0.0100*	0.0112**	0.0163**	0.0075	0.0113*
	(0.0059)	(0.0059)	(0.0051)	(0.0053)	(0.0056)	(0.0058)
Total Experience, squared	4.1×10^{-5}	4.1×10^{-5}	-8.0×10^{-5}**	-8.0×10^{-5}**	-1.0×10^{-5}	-2.0×10^{-5}
	(3.0×10^{-5})	(2.9×10^{-5})	(2.4×10^{-5})	(2.4×10^{-5})	(2.6×10^{-5})	(2.6×10^{-5})
Therapeutic Experience	0.0083	0.0098	0.0109	0.0150*	-0.0077	-0.0070
	(0.0086)	(0.0087)	(0.0078)	(0.0078)	(0.0083)	(0.0083)
Scope	-0.1300	-0.150	0.645	0.989**	0.431	0.568
	(0.3899)	(0.394)	(0.442)	(0.477)	(0.563)	(0.571)
Co-development Alliance	0.0259	0.0111	0.349**	0.321**	0.495**	0.479**
	(0.1545)	(0.155)	(0.142)	(0.144)	(0.157)	(0.158)
Number of indications for the compound	0.298**	0.305**	0.142**	0.161**	0.172**	0.179**
	(0.0486)	(0.049)	(0.0336)	(0.0356)	(0.0412)	(0.0417)
Screening Ratio		0.499		2.26**		1.32**
		(0.370)		(0.390)		(0.518)
Constant	1.55**	1.19**	0.443*	-1.41**	0.0530	-1.10**
	(0.283)	(0.388)	(0.2592)	(0.417)	(0.3282)	(0.560)
Observations	1997	1997	1252	1252	849	849
R^2	0.05	0.05	0.09	0.12	0.13	0.14
Percent correctly predicted	69.3	69.7	69.8	72.6	70.9	71.4

Notes: Dependent variable is one if an indication successfully completes the development stage, and zero otherwise. Standard errors are in parentheses. Indicator variables are included for therapeutic categories. ** = significantly different from zero at the 5-percent level; * = significantly different from zero at the 10-percent level.

Table 5: Experience-based Economies of Scale and Scope With Firm Fixed Effects

	Phase 1	**Phase 2**	**Phase 3**
Total Experience	0.0127	-0.0509*	-0.0036
	(0.0174)	(0.0281)	(0.0193)
Total Experience, squared	-1.5×10^{-4}	9.2×10^{-4}	6.6×10^{-5}
	(1.4×10^{-4})	(7.1×10^{-4})	(1.3×10^{-4})
Therapeutic Experience	0.0070	0.0125	-0.0037
	(0.0096)	(0.0085)	(0.0093)
Scope	0.117	0.128	-0.0241
	(0.430)	(0.487)	(0.612)
Co-development Alliance	-0.0926	0.324**	0.407**
	(0.181)	(0.159)	(0.179)
Number of indications for the compound	0.297**	0.147**	0.210**
	(0.0495)	(0.035)	(0.0434)
Constant	1.32*	1.22*	0.459
	(0.353)	(0.367)	(0.422)
Fixed effects for the largest firms jointly significant?	No	Yes	Yes
Observations	1997	1252	861
R^2	0.06	0.14	0.20
Percent correctly predicted	71.1	73.6	76.3

Notes: Dependent variable is one if an indication successfully completes the development stage, and zero otherwise. Standard errors are in parentheses. Indicator variables are included for therapeutic categories. We interact Total Experience and Total Experience squared with an indicator variable for the large firms that have a firm fixed effect included. The coefficients on these two variables are not shown above. ** = significantly different from zero at the 5-percent level; * = significantly different from zero at the 10-percent level.

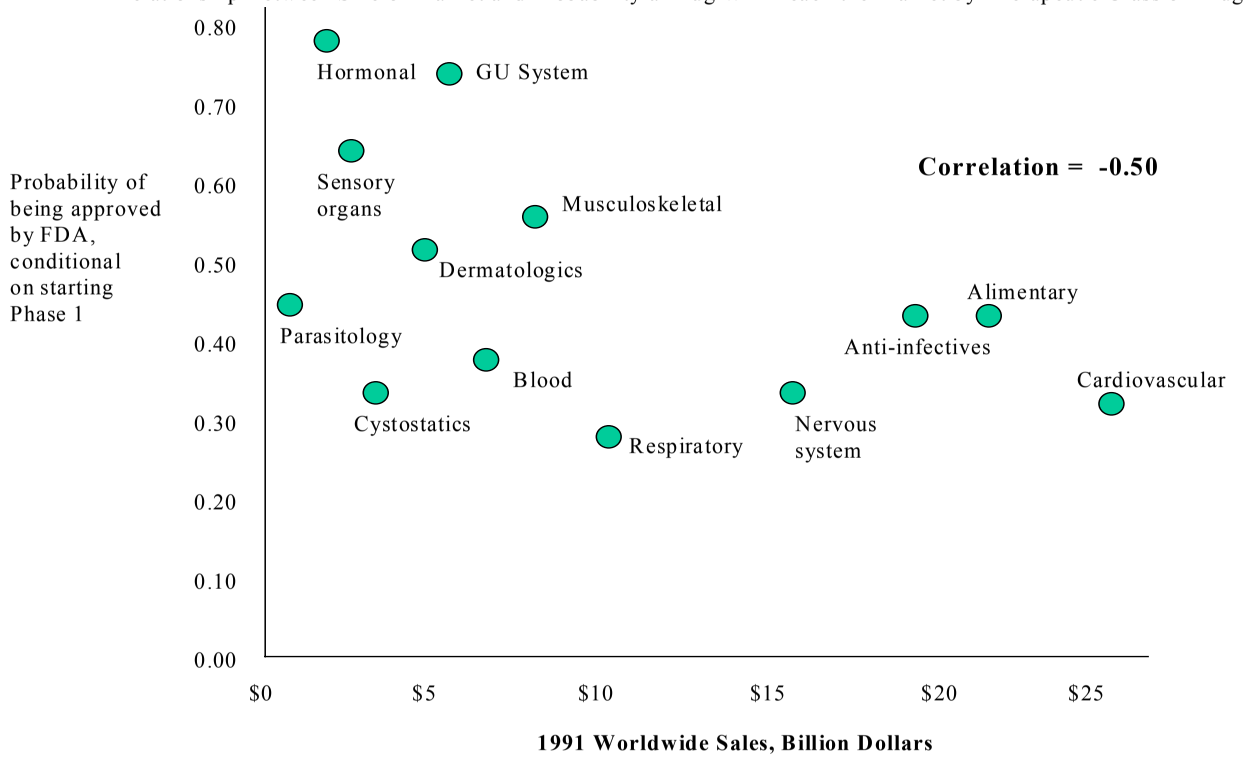
Table 6: Effect of Alliances on Probability of Advancing in a Clinical Trial

	Phase 1		Phase 2		Phase 3	
	(1)	(2)	(3)	(4)	(5)	(6)
Indication originated by small company:	0.525**	0.473**	-0.006	-0.019	0.090	0.091
(large companies are omitted category)	(0.218)	(0.219)	(0.223)	(0.235)	(0.297)	(0.301)
Developed in an Alliance	-0.546**	-0.886**	0.862**	0.895**	0.226	0.171
	(0.257)	(0.305)	(0.298)	(0.359)	(0.338)	(0.402)
- with small licensee		0.512		-0.341		-0.261
		(0.394)		(0.445)		(0.529)
- with large licensee		0.885*		0.174		0.211
		(0.468)		(0.469)		(0.445)
Indication originated by medium-sized company:	0.494**	0.464**	-0.163	-0.299	0.041	0.027
	(0.229)	(0.232)	(0.215)	(0.220)	(0.278)	(0.283)
Developed in an Alliance	0.073	0.041	0.450*	-0.278	0.581**	0.635*
	(0.290)	(0.355)	(0.238)	(0.310)	(0.292)	(0.390)
- with small licensee		1.32		0.439		-0.946
		(1.05)		(0.490)		(0.601)
- with large licensee		-0.038		1.33**		0.100
		(0.397)		(0.348)		(0.396)
Indication originated by large company	0.409	0.404	0.126	0.110	0.471**	0.470**
and developed in an Alliance	(0.252)	(0.252)	(0.215)	(0.215)	(0.221)	(0.221)
Number of conditions	0.321**	0.319**	0.170**	0.173**	0.185**	0.184**
for the compound	(0.049)	(0.049)	(0.035)	(0.035)	(0.041)	(0.042)
Screening Ratio	0.594**	0.629**	1.37**	1.62**	-0.013	0.047
	(0.292)	(0.295)	(0.313)	(0.320)	(0.379)	(0.397)
Constant	0.639**	0.631**	0.059	-0.031	0.470	0.460
	(0.229)	(0.228)	(0.227)	(0.229)	(0.299)	(0.306)
Observations	2057	2057	1275	1275	861	861
R^2	0.06	0.06	0.10	0.12	0.13	0.13
Percent correctly predicted	70.7	71.5	71.1	72.0	70.3	70.6

Notes: Dependent variable is one if an indication successfully completes the development stage, and zero otherwise. Large originators and medium-sized licensees are the omitted groups. A small firm has three or fewer drugs in development during the sample period; a medium-sized firm has between four and 24, and a large firm has 25 or more. Indicator variables are included for therapeutic categories. ** = significantly different from zero at the 5-percent level; * = significantly different from zero at the 10-percent level.

Figure 1

Relationship Between Size of Market and Probability a Drug Will Reach the Market by Therapeutic Class of Drug



Source: Adis, Med Ad News.

All in-text references underlined in blue are linked to publications on ResearchGate, letting you access and read them immediately.

Figure 2

Effect of the Experience of the Originator on the Predicted Probability an Indication Will Advance