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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 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.


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## 1. 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% of global sales in 2000 for the US research-based pharmaceutical industry, compared to 10.5% for computer software, 8.4% for electrical and electronics firms and 3.9% 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 US$ 802 million (DiMasi et al., 2003). 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. For each new compound that is approved, roughly five enter human clinical trials and 250 enter preclinical testing. Thus, a key management challenge in increasing R&D productivity is to raise the percentage of compounds that succeed in clinical trials. Success rates are also critical in valuing an individual drug, a company's pipeline of drugs and a company as a whole.

Relatively little is known about the determinants of success rates in pharmaceutical R&D. Most of the published data come from the Tufts Center for Drug Development (CSDD), using a proprietary database that 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 et al. (1991) and DiMasi (2000, 2001) report estimates of average success rates by development phase, by therapeutic category and for self-originated versus in-licensed drugs. Henderson and Cockburn (1996) and Cockburn and Henderson (2001) use proprietary data from 10 pharmaceutical firms to test for economies of scale and scope at the level of the firm and research program, for the period 1961–1990.

These studies largely predate recent developments that changed the nature of R&D, including the biotech and genomics revolution and the increasing importance of small and medium-sized firms; the horizontal mergers between large pharmaceutical firms that were supposed to improve R&D productivity through economies of scale and scope; and the growth of contract research organizations (CROs) that enable firms to outsource their clinical trials. Thus, the average success rates in DiMasi's studies and the scale and scope relationships identified by Henderson and Cockburn may not reflect current conditions. These studies also do not examine the role of biotech–pharmaceutical alliances.

In this paper, we develop more current and more detailed estimates of R&D success probabilities, by therapeutic category and firm size, using data from Adis International on over 1900 compounds developed in the US by over 900 firms between 1988 and 2000. Specifically, we estimate the effect on phase-specific success rates of a firm's overall

[1] Firms must file an Investigational New Drug (IND) application 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; phase 3 trials test whether the drug is effective in a large sample of patients with the targeted disease. Upon completing phase 3, a company files a New Drug Application (NDA) with the FDA for regulatory review and approval.

experience; its experience in the relevant therapeutic category (e.g., cardiovascular disease); 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 cumulative number of compounds with which the firms was involved as an originator or a licensee prior to the clinical trial of interest. Learning-by-doing may produce general and category-specific skills in designing and managing trials, and improved relationships with clinicians and regulators, thereby contributing to trial success rates.

A second 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 drug discovery and the types of drugs that emerge. Small firms, which have played a key role in developing these new technologies, often develop drug leads and then out-license these leads to large pharmaceutical firms, who then take the drug through development, clinical trials and ultimately regulatory approval. One rationale for these alliances is that the experience of large firms adds sufficient value to offset the costs of operating the alliance (Nicholson et al., 2003). We test whether alliances do in fact enhance success probabilities and how any effects vary depending on the experience of the licensing partners.

For phase 1 trials, which are small and relatively straightforward, we find that returns to experience are 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). We find no evidence that scale improves productivity beyond a threshold size, although economies of scale and scope in R&D have often been cited as a major reason for recent horizontal mergers between large pharmaceutical firms. We also find no evidence that a drug's success probabilities are associated with the firm's therapeutic category-specific experience. However, the therapeutic experience of the entire industry is positively associated with the likelihood that a drug in that category will successfully complete phase 1, and negatively associated with the likelihood it will complete phase 2 and phase 3. The phase 1 result suggests that there may be category-specific spillover learning across firms in safety testing. The phase 2 and phase 3 results could reflect an increase in FDA approval standards as a category becomes crowded with candidate products; the results could also reflect diminishing scientific returns at the external margin, that is, finding new drugs in crowded categories requires going after increasingly risky prospects. Finally, drugs developed by firms whose experience is focused rather than broad (diseconomies of scope) are more likely to complete phase 3 successfully.

Our results confirm that drugs developed in alliances are more likely to succeed in clinical trials, especially for phase 2 and phase 3, and when the licensee has more drug development experience than the originator. Thus, any "lemons" or moral hazard effects associated with out-licensing appear to be dominated by gains from trade. Large firms have higher success rates on in-licensed compounds than on compounds that they originate in-house, which is further evidence against allegations of moral hazard on licensed products.[2] These results

[2] This is consistent with DiMasi (2001) and Arora et al. (2000), but not Pisano (1997).

are conditional on the existence of an alliance; our data are insufficient to analyze alliance formation, choice of partners or effects of specific contractual terms.

More generally, 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 a 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 behavior.[3] However, a complete model of dynamic equilibrium is beyond the scope of this paper.

## 2. Determinants of R&D productivity: theory and previous literature

### *2.1. Experience and economies of scale and scope*

Several of the recent large horizontal mergers in the pharmaceutical industry have been rationalized at least in part by economies of scale in R&D, but evidence is limited on whether such economies exist and, if so, over what range. Henderson and Cockburn (1996) use up to 30 years of data from 10 U.S. and European pharmaceutical firms, which collectively accounted for 25% of worldwide pharmaceutical research, to test for returns to scale and scope in drug discovery/research and knowledge spillovers within and between firms. Their dependent variable is the number of patents filed by a disease-specific research program, such as depression or anxiety. For drug discovery, they find evidence of returns to scale (defined as total research spending) at the firm level but not at the research program level. Firms with diversified research activities (number of programs with expenditures over US$ 500,000 per year) also appear to file more patents, providing support for economies of 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) use data from the same 10 firms to examine scale and scope economies in the clinical development phase of R&D. They measure scale as the firm's total development expenditures and scope as the number of research programs on which the firm's spending averages at least US$ 1 million per year. Their unit of observation is a development project that has started phase 1 trials 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 scale within a therapeutic category, but no evidence of overall scale economies. When firm fixed effects are included, however, the scope measure becomes statistically insignificant, which raises the possibility that firm-specific strategies, rather than breadth of development activities, explain the differential success rates. Moreover, since much of the scale and scope variation is within firms as they grew over time, rather than between firms, measures of scale and scope economies may be contaminated by technological and other time-related changes.

[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.

### 2.2. Alliances

In our sample a majority of drugs in phase 2 and phase 3 are developed in an alliance, but the role of alliances in R&D productivity is not examined in either of the two Henderson and Cockburn studies. Theory suggests several reasons why firms may form alliances and hence why alliances may affect R&D productivity (see Kogut, 1988, for a summary). First, simple theory of contracting over property rights predicts that an originator firm will pursue drug development with a partner if the expected benefits exceed the transactions and other costs of licensure. Powell and Brantley (1992) argue that a single biotechnology firm rarely has all the necessary skills and organizational capabilities to succeed. Since drug development technology is changing rapidly and the sources of knowledge are dispersed across many companies, biotech firms will have strong incentives to enter into an array of alliances (Powell et al., 1996). This gains-from-trade theory predicts that alliances should have a positive effect on success probability, particularly when relatively inexperienced firms outlicense to relatively experienced firms, and for the more complex phase 2 and phase 3 trials. A second, not mutually exclusive hypothesis is 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 et al., 2003). This motive for alliances may have a positive effect on success probabilities if access to financing enables a biotech to conduct larger or better-designed trials.

The potential positive effects of alliances may be mitigated by the potential negative effects of moral hazard and adverse selection. Moral hazard with respect to effort may occur because 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% of gross sales as a royalty. The adverse selection or "lemons" theory articulated by Pisano (1997) posits that small firms take advantage of asymmetric information to out-license their least promising compounds, retaining their more promising candidates to develop independently. A market for alliances could still exist if alliance prices are appropriately reduced to reflect this adverse selection risk faced by in-licensing firms. Contractual terms are often designed to deter shirking and selection incentives, through milestone payments, royalties and other contingent or back-loaded forms of payment to the licensor. Both the moral hazard and the lemons hypotheses predict a negative effect of co-development on a drug's success probabilities, if these effects are large enough to dominate any gains from pooled experience and better financing.

These theories of alliances cannot explain why large firms would out-license, since they presumably have greater experience and lower financing costs than smaller firms. There are several reasons why large firms might out-license compounds. First, due to the stochastic nature of drug R&D, a firm may find itself with more potential compounds ready for development than can be accommodated by its in-house personnel. Handling this temporary excess by out-licensing avoids the fixed costs of hiring more personnel. Second, large companies typically apply a minimum threshold of expected sales to compounds that they develop in-house. Compounds that fall below this threshold may be out-licensed to smaller companies that apply lower expected sales thresholds; this enables the large firm to retain some stake in the compound, while committing fewer resources than would

be required for in-house development. Third, a large firm may enter a development and marketing alliance with another large firm for compounds with very large market potential in order to share the marketing expense and/or diversify risk on the very large marketing investment required.

The empirical evidence on the impact of drug development alliances is mixed. Lerner and Tsai (2000) find that alliances formed during periods of unfavorable public and private equity markets 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 et al. (2003) 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. Powell et al. (1999) find that R&D alliances help biotech firms establish a position within a network of firms, which in turn generates incremental patents, sales and non-operating income. All of the above studies use more limited data sets and none examine whether the performance of alliances varies according to the experience of the originating and licensing companies, as we do in this paper.

### *2.3. Hypotheses*

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

(1) Drugs developed by firms with relatively high overall and therapeutic-category specific experience are more likely to advance in clinical trials (economies of scale).
(2) Drugs developed by firms with relatively diversified experience across therapeutic categories are more likely to advance in clinical trials (economies of scope).
(3) Alliances increase R&D productivity, on average. Productivity gains are expected to be greater for alliances between inexperienced and more experienced firms than for alliances between two relatively experienced firms; and for the more complex phase 2 and phase 3 trials than for simple phase 1 trials.

## 3. Data and methodology

Our principal data source is the R&D Insight database from Adis International. It includes 1910 compounds developed by pharmaceutical and biotech firms in the US between 1988 and 2000, with most of the observations occurring after 1994. The data set contains information on characteristics of the compound, including allocation to one or more of 13 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). Sample means and standard deviations are presented in Table 1.

Our unit of analysis is a specific indication for which a drug is being developed, rather than a drug or development project.[4] Since the FDA requires clinical trial evidence to estab-

[4] By contrast, Cockburn and Henderson (2001) and Henderson and Cockburn (1996) analyze output of an entire research program, which typically includes multiple compounds, each for multiple indications.

Table 1
Sample means and standard deviations

| Observations (indications) | Phase 1 | Phase 2 | Phase 3 |
|---|---|---|---|
| | 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 |
| Drug is developed in an alliance | 0.494 | 0.547 | 0.621 |
| Average number of indications per compound | 3.35 (2.88) | 3.05 (2.50) | 2.98 (2.23) |
| Firm's phase-specific Total Experience | 7.26 (7.78) | 8.72 (8.10) | 9.38 (7.77) |
| Firm's phase-specific Therapeutic Experience | 5.44 (5.99) | 6.44(6.18) | 7.51 (6.50) |
| Industry's phase-specific Therapeutic Experience | 471 (375) | 513 (459) | 436 (311) |
| Scope of firm's R&D (HHI index across Therapeutic categories) | 0.298 (0.260) | 0.247 (0.220) | 0.216 (0.192) |
| Screening Ratio (percentage of pre-clinical drugs that begin phase 1) | 0.616 (0.258) | 0.610 (0.228) | 0.608 (0.209) |

*Note*: Standard deviations are in parentheses for each continuous variable.

lish efficacy for each approved indication, an indication represents the most disaggregated unit of R&D output. Alliances between companies may also cover some but not all of a compound's indications. Since the indications that appear in our sample depend on strategic choices made by firms, the regression results should be interpreted as being conditional on a firm choosing to proceed with a clinical trial.[5] We include in our regression analysis the number of indications for which a compound is or has been tested. This variable may be a proxy for unmeasured "quality," assuming that more promising compounds are pursued for more indications and/or that success for a prior indication means that the compound has passed certain safety tests. 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. The Adis database assigns the same therapeutic categories to all indications for which a compound is being developed. We report robust standard errors to control for correlation of unobserved characteristics across indications for a given compound.

[5] A complete model of the R&D process would treat as endogenous the number of indications targeted, in addition to the existence of an alliance and the partner(s) chosen. Our data are insufficient to estimate such a complete model. We therefore, treat the number of indications, the existence of an alliance and type of partner as predetermined. All regression coefficients should be interpreted as conditional on these prior decisions.

We perform a series of logistic regressions to analyze the determinants of R&D productivity. Specifically, 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.[6] Our sample consists of 2057 observations for phase 1, 1275 observations for phase 2 and 861 observations for phase 3.

The data suffer from both left and right censoring. Left 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 and incomplete reporting of drugs that fail in phase 1.[7] By including a drug only when we observe that it begins a development stage, we mitigate the potential survival bias that could result from incomplete reporting.

Right 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 phase 1 and phase 3, and 6 years for phase 2. For example, if an indication entered phase 1 or phase 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 phase 1 or phase 3 in or after 1996 or phase 2 in or after 1995 and contain no subsequent outcomes information are excluded from our regression analysis.

We define a firm's overall experience (Total Experience) as the (depreciated) total number of compounds in a particular phase (i.e., phase 1, phase 2 or phase 3) with which the firm was involved, either as an originator or a licensee, between 1988 and the date of the clinical trial of interest.[8] The firm's Total Experience thus varies over time and is phase-specific.[9] For the results reported, we depreciate experience by 10% per year to reflect the likely depreciation

[6] Information on the date at which an indication enters and completes a trial phase is incomplete. We therefore, cannot estimate the probability of approval of the first indication, similar to DiMasi et al. (2003) or estimate a hazard model of time to phase completion.

[7] Since Adis obtains its information from public announcements, interviews and other sources, it is likely to track 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. In that case, drugs that were discontinued in phase 1 may be underrepresented in the database, relative to drugs that completed phase 1.

[8] 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 clinical trials, regardless of whether the compound failed or succeeded, such bias should be minor.

[9] Adis updates firm names to reflect merger and acquisition information. 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 firm experience variable, the effect should be small because 83% of the observations in our analysis are from the 1996–2000 period, hence occur after many of the large mergers. To the extent that we overestimate experience of the largest firms, we may underestimate returns to experience for these firms.

of knowledge within a firm; results with undepreciated experience were very similar. The regressions include dummy variables for the year in which an indication exited a phase. These variables control for the secular increase in experience over the sample period, as well as any other time-specific effects such as changes in the FDA's approval standards or changes in types of compounds being developed. 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.

Our 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 (Myers 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.

In order to examine whether experience in a therapeutic category 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 category of interest, separately for phase 1, phase 2 and phase 3. 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 also include a measure of total Industry Therapeutic Experience by phase and therapeutic category to test for spillover effects of experience across firms. If such cross-firm knowledge spillovers are positive, the effect of Industry Therapeutic Experience is expected to be positive. Conversely, success probabilities may decline in crowded therapeutic categories, either because firms must pursue progressively more difficult or risky prospects once the low hanging fruit in a category have been picked, or because the FDA implicitly requires higher benefit/risk ratios to approve new drugs in crowded categories.

To measure experience-based economies of scope (Scope), we define a Herfindahl–Hirschman index (HHI) as the proportion of the firm's compounds in each therapeutic category, squared and summed across all therapeutic categories in which the firm has been active.[10] Thus our experience and scope measures are based on numbers and distributions of compounds, whereas Cockburn and Henderson (2001) measure scale based on a firm's R&D expenditures and scope as the number of development projects with average annual

[10] 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, 1988).

R&D expenditures in excess of US$ 1 million. Since we do not have expenditure data, we unfortunately cannot compare the predictive performance of these two approaches to measuring scale and scope.

Our data on alliances are from the three databases: Adis' R&D Insights, Windhover Information and Pharmaprojects. 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.[11] 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 the subject of alliances. We create separate alliance indicator variables based on the experience of the originator firm and the licensee to test whether the effect of alliances varies by experience of either party. Our alliance databases do not report contractual terms in sufficient detail to permit testing the effects of specific assignment of rights on outcomes.

Estimating the effects of alliances on R&D success requires caution because alliances are formed by choice. If selection occurs based on unobserved (to the econometrician) drug characteristics, then our estimated effect of an alliance on the likelihood a drug will advance may not be the true causal effect. 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 the stringency of their review criteria before taking a drug into human trials. On 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, researchers in large firms may apply less objective evaluation to their own compounds than that applied by financial markets to small firms seeking external funding. In order to control for the unobserved quality of a firm's compounds, due either to the firm's capabilities and/or its stringency in screening compounds prior to clinical trials, we calculate for each firm a Screening Ratio. This variable is defined as the number of compounds a firm takes into clinical trials divided by the sum of its compounds in clinical trials plus preclinical compounds that do not enter trials.[12] The Screening Ratio can range from zero to one. If product quality varies randomly across firms but some firms set higher standards in screening compounds to take into clinical trials, then Screening Ratio would be inversely related to success probability. However, if firms differ more in the underlying quality of their drugs than in the expected success probability they require to take a compound into clinical trials, then a low Screening Ratio would indicate

[11] 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 out-license to large firms than vice versa. When more than one licensee is listed, we assign licensee status to the largest firm.

[12] Drugs in the preclinical stage after 1998 are not included in the Screening Ratio because we do not observe these drugs for a long enough time to know whether they will enter clinical trials.

that a firm's preclinical drugs have relatively poor prospects. In that case Screening Ratio would be positively related to success probability. It is also possible that some firms take a larger fraction of their preclinical compounds into clinical trials because they are more competent and hence anticipate an above average success rate. In that case, Screening Ratio could be endogenous and could be positively correlated with Total Experience. In fact, the correlation between Screening Ratio and Total Experience is 0.19, plausibly because many small firms with only one or two compounds have a Screening Ratio of one. Nevertheless, as a check on bias in other coefficients due to possible endogeneity of Screening Ratio, we also estimate the equations without Screening Ratio.

## 4. Results

We begin by examining the extent to which development success rates vary across therapeutic categories. In Table 2 we report marginal effects from separate logit regressions for phase 1, phase 2 and phase 3, where the only regressors are therapeutic category indicator

Table 2
Marginal effects of therapeutic category indicators (in percentage points)

| | Phase 1 | | Phase 2 | | Phase 3 | |
|---|---|---|---|---|---|---|
| | Marginal effect | Standard error | Marginal effect | Standard error | Marginal effect | Standard error |
| A: Antithrombotic | 0.42 | (2.0) | 3.6 | (3.4) | −7.6 | (5.2) |
| B: Blood | 0.40 | (2.5) | 3.3 | (4.2) | −19** | (6.8) |
| C: Cardiovascular | 0.45 | (2.0) | −8.4** | (3.9) | −18** | (5.1) |
| D: Antipsoriatics | 3.8* | (2.1) | 1.4 | (4.0) | 2.9 | (5.7) |
| G: Urologics and contraceptives | 8.3** | (1.8) | 16** | (3.7) | 13** | (5.2) |
| H: Hormonal preparations | 5.9 | (4.9) | 21** | (5.5) | 21** | (8.4) |
| J: Antivirals | −2.1 | (1.9) | 1.7 | (3.3) | −2.2 | (4.7) |
| L: Cytotoxics | 4.4** | (1.5) | −12** | (2.8) | −19** | (4.2) |
| M: Antiinflammatory | 2.9 | (2.1) | 5.0 | (3.5) | 3.2 | (4.8) |
| N: Nervous system | 0.41 | (1.9) | −0.6 | (3.3) | −22** | (4.9) |
| P: Parasitology | −0.63 | (4.7) | 9.6 | (7.3) | 0.45 | (14) |
| R: Respiratory system | 5.3** | (1.9) | −20** | (4.8) | −18** | (7.4) |
| S: Carbonic anhydrase | 5.9** | (2.6) | 13** | (4.5) | 8.0 | (7.5) |
| Mean of the dependent variable | 88.2 | | 72.5 | | 61.2 | |

*Note*: Robust standard errors are in parentheses. The marginal effect for say category A is calculated as Prob[$Y = 1 \mid A = 1, \boldsymbol{X}^*$] − Prob[$Y = 1 \mid A = 0, \boldsymbol{X}^*$], where the $\boldsymbol{X}^*$ vector includes all variables evaluated at their means except the category A dummy, which is set to either 1 or 0. The marginal effect is thus the predicted probability of success for a drug with a category A indication, relative to the mean probability for drugs with no category A indication. With this approach the marginal effects need not average out to zero. There is no omitted therapeutic category in the regression because many compounds target multiple categories and hence the therapeutic category indicators are not mutually exclusive.

* Significantly different from zero at the 10% level.

** Significantly different from zero at the 5% level.

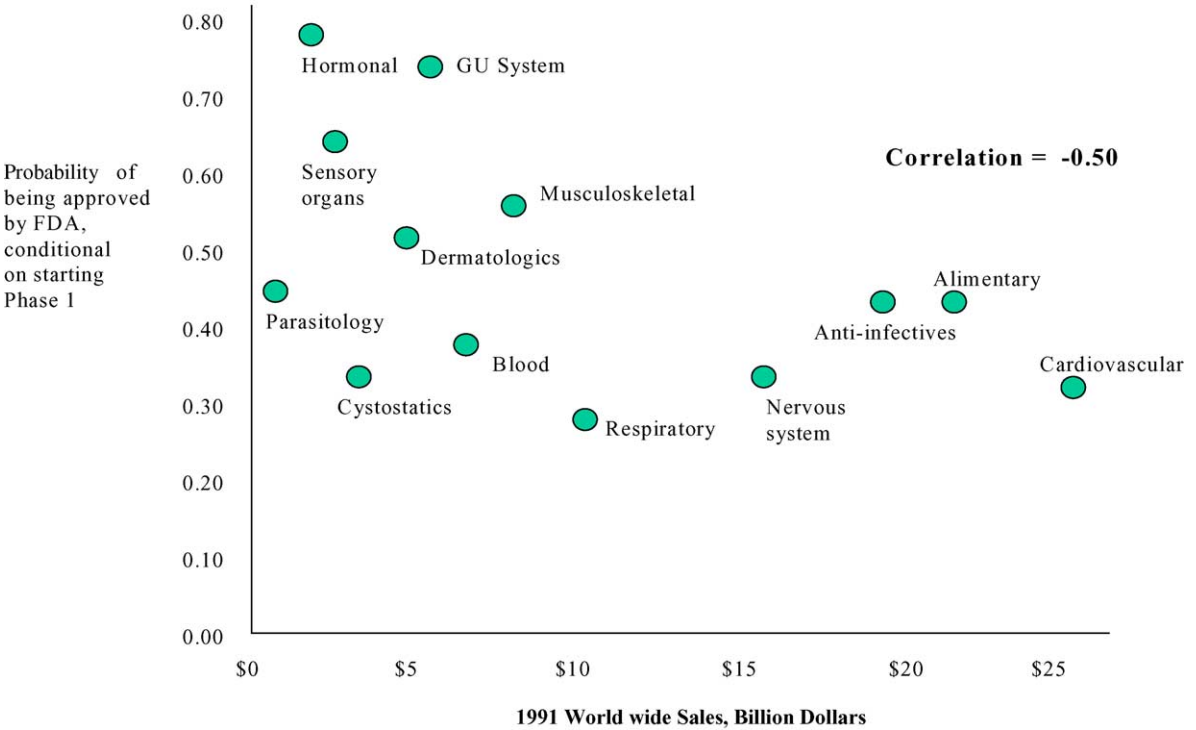
variables. Since the therapeutic categories are not mutually exclusive – a compound can target multiple therapeutic categories – all 13 therapeutic category indicators are included in the regressions. The marginal effects report the change in the probability that an indication will complete a phase if it targets that therapeutic category, relative to the overall average probability, measured in percentage points.

The predicted probability that an indication will advance differs from the overall average for five 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, is 22 percentage points below the sample average (61.2%) for central nervous system drugs and 21 percentage points above the average for hormonal preparations.

To calculate the predicted probability that the FDA will approve an indication, conditional on starting phase 1, we multiply the three phase-specific predicted probabilities of success for each therapeutic category. Drugs for respiratory indications have the lowest predicted probability of being approved (30%), whereas hormone preparations have the highest predicted probability (78%) (see Fig. 1). These large differences in success probabilities across therapeutic categories might seem inconsistent with a model in which firms initiate R&D until the expected return is equalized across therapeutic categories and is equal to the risk-adjusted cost of capital, unless offsetting differences exist across categories in costs or in expected revenues, conditional on reaching the market. In fact, total market size varies significantly across therapeutic categories. Given such variation, equalization of expected returns across categories could occur through several competitive mechanisms, including: smaller market shares per drug in large categories; lower prices in large categories, due to more intense price competition; shorter life-cycle of sales in large categories, due to cannibalization by successive entrants, as hypothesized by Acemoglu and Linn (2003); and lower success probabilities and/or higher costs of trials in large categories. Lower success probabilities could occur if either technological hurdles to creating new compounds rise once the easy compounds in a category have been developed, or if the FDA implicitly raises the standards required of new compounds in crowded categories.

Testing between these alternative hypotheses is beyond the scope of this paper; however our data do suggest the last two factors – lower success probabilities and higher costs in large therapeutic categories – play a role.[13] In Fig. 1, we plot the predicted probability that a drug will be approved in each therapeutic category, conditional on entering clinical trials, 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 our sample compounds were in discovery testing. In Fig. 1, the correlation between the probability that a drug will reach the market and sales in the therapeutic category is −0.504 at the sample mean

[13] Differences in FDA requirements may contribute but are unlikely to fully explain the observed differences in success rates across classes. The FDA has Priority Review and Fast Track approval procedures for new drugs and biologics that are intended to treat life-threatening diseases and address unmet medical needs. These procedures are intended to affect the speed of review, not the probability of success. Success probabilities could be affected if the FDA accepts higher risks or lower benefits for diseases with no existing treatments. However, such diseases are much more narrowly defined than our therapeutic categories and probably exist in most categories.




Source: Adis, Med Ad News.

Fig. 1. Relationship between size of market and probability a drug will reach the market by therapeutic class of drug.

probabilities, with a *p*-value of 0.079. Using 2001 worldwide sales by therapeutic category, the correlation is −0.642 with a *p*-value of 0.018. Thus, indications targeting relatively large categories (e.g., respiratory therapy, central nervous system, alimentary and cardiovascular) have relatively low predicted success probabilities. In other words, firms appear to be willing to develop drugs with a lower probability of success in therapeutic categories with greater sales potential. Firms also appear to be willing to incur higher costs on 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. This evidence suggests that competition may reduce expected rents across categories on both the extensive margin (willingness to take on riskier conditions/drugs) and on the intensive margin (willingness to spend more per drug program).

Our indication-specific predicted probabilities of approval, conditional on entering human trials, are somewhat higher than the 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 as a control variable.

### *4.1. Experience-based economies of scale and scope*

We next test for evidence of experience-based economies of scale and scope in drug development in Table 3. In phase 1 there is a convex relationship between the probability an indication will advance to phase 2 and the originating firm's Total Experience (a contemporaneous measure of the number of phase 1 compounds the firm developed, either as an originator or as a licensee, between 1988 and the clinical trial of interest). As shown in Fig. 2, the predicted probability that an indication will advance if developed by a firm that has prior experience with a single phase 1 drug is 94%. This predicted probability declines gradually with experience to a minimum of 90% for firms that have developed 15 phase 1 drugs and then increases slightly thereafter. Therefore, a firm's experience has a small economic effect in phase 1: at the sample mean (7.3 phase 1 drugs), a unit increase in a firm's Total Experience is associated with a 0.5 percentage point reduction in the probability an indication will advance from a phase 1 to a phase 2 trial and this marginal effect is significantly different from zero at a 10% level.[14] Since a negative return to experience seems implausible, this may reflect more experienced firms applying more stringent scientific and economic screens in order to take a compound forward.

The returns to Total Experience are positive and more economically substantial for the more advanced clinical trials than for phase 1. In phase 2, the effect of Total Experience

[14] The marginal effect of a unit increase in Total Experience incorporates the coefficients on both the linear and quadratic Total Experience terms. The standard error of the marginal effect is calculated using the Delta Method.

Table 3
Experience-based economies of scale and scope in pharmaceutical/biotech drug development

| | Phase 1 | | Phase 2 | | Phase 3 | |
|---|---|---|---|---|---|---|
| | Marginal effect | Standard error | Marginal effect | Standard error | Marginal effect | Standard error |
| Firm's Total Experience | −0.49* | (0.29) | 1.2* | (0.61) | 2.0** | (1.0) |
| Firm's Therapeutic Experience | 0.051 | (0.17) | 0.16 | (0.38) | −0.35 | (0.47) |
| Industry's Therapeutic Experience | 0.0047* | (0.0025) | −0.011** | (0.0060) | −0.021** | (0.010) |
| Scope (HHI across therapeutic categories) | −0.98 | (2.5) | 12 | (7.6) | 23* | (12.0) |
| Co-development alliance | 0.44 | (1.1) | 9.0** | (2.6) | 14** | (3.8) |
| Number of indications for the compound | 2.7** | (0.31) | 2.8** | (0.66) | 4.1** | (1.0) |
| Screening Ratio | 4.9** | (2.1) | 32** | (5.7) | 9.4 | (9.1) |
| Observations | 2057 | | 1275 | | 861 | |
| Pseudo $R^2$ | 0.12 | | 0.12 | | 0.15 | |
| Percent correctly predicted | 74.6 | | 74.0 | | 75 | |
| Mean of the dependent variable | 88.2 | | 72.5 | | 61.2 | |

*Notes*: Dependent variable is one if an indication successfully completes the development stage, and zero otherwise. The regressions also include a full set of therapeutic category and year indicators. The marginal effect is the change in the probability an indication will advance in clinical trials associated with a unit increase in the independent variable, holding the other regressors at their mean values, measured in percentage points.

* Significantly different from zero at the 10% level.

** Significantly different from zero at the 5% level.

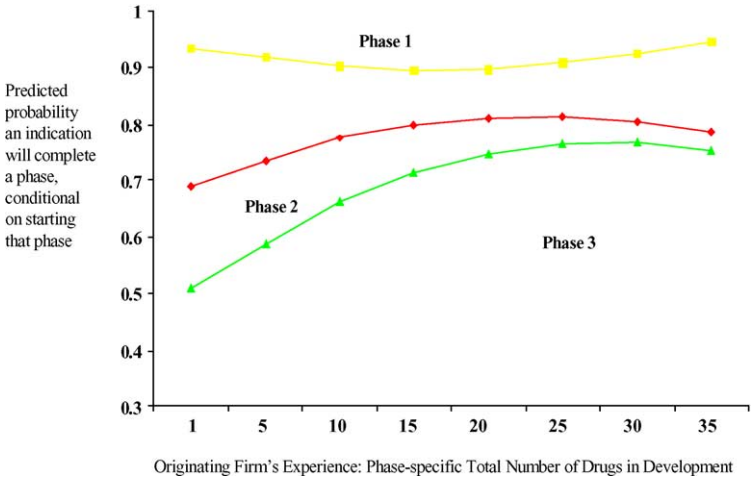



Fig. 2. Effect of the experience of the originator on the predicted probability an indication will advance.

on the likelihood of completing the phase is concave. The predicted probability of a phase 2 success for a firm that has previously participated in only one phase 2 trial is 69% (see Fig. 2). This predicted probability increases with the originator's experience to a maximum of 81% for a firm with experience in 25 phase 2 compounds and then decreases thereafter. At the sample mean (8.7 phase 2 drugs), a unit increase in Total Experience is associated with a 1.2 percentage point increase in the probability an indication will successfully complete a phase 2 trial and the marginal effect is significant at a 10% level.

In phase 3, the effect of Total Experience is concave as in phase 2. The predicted probability that an indication will complete phase 3 if the originating firm has previously developed a single phase 3 drug is 51% versus 81% for a firm that has developed 30 phase 3 drugs (see Fig. 2). At the sample mean (9.4 phase 3 drugs), a unit increase in a firm's Total Experience is associated with a 2.0 percentage point increase in the probability an indication will successfully complete a phase 3 trial and this marginal effect is significant at a 5% level.[15]

Our result that a firm's development experience does not substantially affect the likelihood that an indication will complete phase 1 but has a considerable effect in phase 2 and phase 3, is 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 phase 3 trials, which require perfecting the dosage and establishing statistical evidence of efficacy in large patient samples.

We find no evidence of returns to therapeutic experience. Controlling for Total Experience, category-specific Therapeutic Experience (number of phase 1, phase 2 or phase 3 compounds the originator firm had developed in the same therapeutic category as the compound being evaluated) is insignificant in all three phases.[16]

The total Industry Therapeutic Experience in a therapeutic category is positively associated with the likelihood that a drug in that category will successfully complete phase 1 and negatively associated with the likelihood it will complete phase 2 and phase 3. Since year and therapeutic category indicators are included in the regressions, the coefficient on Industry Therapeutic Experience is identified by within-category changes in experience over time. The positive phase 1 marginal effect suggests positive knowledge spillovers across firms in safety testing. The negative phase 2 and phase 3 marginal effects are consistent with the hypotheses that either firms pursuing new drugs in crowded categories must go after more risky targets and/or that the FDA raises approval standards in therapeutic categories with multiple existing compounds. The phase 2 and phase 3 results are also consistent with our earlier finding that indications targeting categories with relatively large sales have relatively low success probabilities.

For phase 1 and phase 2, we find no evidence of returns to experience-based Scope, as measured by a Herfindahl index (HHI) of the squared shares of compounds in each therapeutic category in which the firm is active. In fact, the evidence suggests negative

[15] These results are robust to excluding Screening Ratio from the regressions, except that for phase 2 the marginal effect of Total Experience is insignificant when Screening Ratio is omitted. As noted earlier, the correlation between Screening Ratio and Total Experience is −0.19.

[16] Therapeutic and Total Experience are highly positively correlated. Omitting Therapeutic Experience has very little effect on the magnitude of the regression coefficients, although Total Experience is measured more precisely in such specifications.

returns to experience-based scope in phase 3. In other words, firms that focus 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 3. A one standard deviation increase in the HHI is associated with a 4.4 percentage point increase in the likelihood that an indication will complete a phase 3 trial. By contrast, Cockburn and Henderson (2001) find 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.[17] In particular, it is plausible that specialization increases expertise for the small and medium size firms that dominate our sample but were excluded from the Cockburn and Henderson sample.

In Table 3, 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. The marginal effect for Screening Ratio is positive and significant for phase 1 and phase 2; firms that take a relatively large proportion of their preclinical drugs into human trials are more likely to experience successes in these trials. This suggests that this variable is measuring unobserved characteristics of a compound or unobserved ability of firms' managers, rather than different stringency levels of firms' internal review processes. The fact that coefficients on other variables are robust to excluding Screening Ratio indicates that these unobserved characteristics are not highly correlated with our measured variables.

Although the coefficients on the year indicator variables are jointly significant in all three phases, few of the individual coefficients are significantly different from zero and there is no clear trend in success rates over time.

We next explored whether large pharmaceutical firms differ in their productivity, conditional on their experience and the scope of their development activity. In regressions not reported here (available from the authors), we add to the regressions reported in Table 3 a vector of firm fixed effects for the 22 firms with 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 its quadratic with a Large Firm indicator variable for firms that developed 25 drugs or more, to test for differential effects of experience between small and large firms.

There is very little difference across firms in performance in phase 1. Only one of the 22 firm coefficients is significantly different from zero at the 10% level 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. In phase 2, the firm fixed effects are jointly significant and seven of the 22 firm coefficients are significantly different from zero at the 10% level. The predicted probability that an indication will complete phase 2 varies by eight percentage points among the seven firms that have significant firm fixed effects. As in phase 1, the coefficients on experience for relatively small firms are insignificant.

[17] Cockburn and Henderson (2001) use a sample of 10 firms for 1961–1990, 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 1000 firms includes many more observations on firms in the small- and medium-size range, where returns to experience are likely to be most important.

Firm fixed effects are also jointly significant in phase 3. Seven of the 22 firm indicators are significantly different from zero and the marginal effects for these firms range from 13 to 34 percentage points. As in phase 1 and phase 2, the Total Experience measures are very imprecisely estimated and become insignificant once we control for firm fixed effects.

### *4.2. Alliances*

In Table 3, indications that are developed in an alliance are no more likely to complete phase 1 than drugs that are developed independently by the originating company. However, co-developed indications 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 9.0 percentage points higher than an indication that is developed by its originating company, other things equal. In phase 3, co-developed indications have a 14.1 percentage point higher predicted probability of advancing.

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 the distribution of alliances by phase, shown in Table 4. Table 4 reports the number and percentage of indications (e.g., anxiety) for which a drug is being developed that are out-licensed, by

Table 4
Alliance activity by development phase and experience of originator and licensee

| Experience 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 |

*Note*: A small firm had three or fewer drugs in development (drugs they originated plus drugs they in-licensed) during the 1988–2000 sample period; a medium-sized firm had between four and 24, and a large firm had 25 or more. There are 776 small firms in the sample, 163 medium-sized firms and 22 large firms.

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-size firms to form an alliance. Recall that we define a small firm as one that had three or fewer drugs in development (drugs they originated plus drugs they in-licensed) during the 1988–2000 sample period; a medium-size firm as one with between four and 24 drugs; a large firm as one with 25 or more drugs. There is no strong pattern of alliances by size of the originator and licensee in phase 1: small firms often form alliances with other small firms (112 indications in panel A of Table 4) and large firms sometimes form alliances with small firms (84 indications in panel A of Table 4). For phase 2 and phase 3, a larger percentage of indications are co-developed and the licensees are more often medium and larger firms. Fifty-five percent and 62% 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).

The data in Table 4, are generally consistent with the gains-from-trade theory: small and medium-size firms appear to have the skills and resources necessary to do the relatively simple and inexpensive phase 1 trials, but are more likely to seek a large pharmaceutical partner for the larger, more complex and more expensive phase 3 trials. Almost two-thirds (62.1%) of indications are under co-development by phase 3 and the majority of phase 3 licensees are medium or large firms.

In Table 3, we reported that drugs developed in alliances are more likely, on average, to successfully complete phase 2 and phase 3 trials relative to drugs developed by the originator firm. We next explore in more detail whether the impact of an alliance varies with the experience of the originator and licensee firms. In Table 5, we include indicator variables for indications originated by small and medium-size firms (large firms are the omitted group), and three separate indicator variables if small firms formed an alliance with a small, medium or large firm, and separate indicators if a medium-size firm formed an alliance with a small, medium or large firm. This specification allows us to test whether drugs originated by small and medium-size firms are more likely to succeed if they develop the drugs independently versus in an alliance with a small, medium or large firm. Since we found that experience has a positive effect on the probability that an indication will complete phase 2 and phase 3 trials, we also test whether drugs developed with a large licensee are more likely to advance relative to drugs developed with a small licensee. The regressions in Table 5 also include indicators for the therapeutic categories a drug is targeting and a variable measuring the number of conditions for which the drug is in trials.

For phase 1, drugs that small firms out-license to medium-sized firms have a 9.2 percentage point lower probability of advancing to phase 2 than the average of other indications.[18] 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 with small and medium-sized firms due to moral hazard.

[18] Furthermore, drugs that small firms out-license to other small firms have a lower probability of advancing than drugs that they develop independently.

Table 5
Effect of alliances on probability of advancing in a clinical trial

| | Phase 1 | | Phase 2 | | Phase 3 | |
|---|---|---|---|---|---|---|
| | Marginal effect | Standard error | Marginal effect | Standard error | Marginal effect | Standard error |
| Indication originated by small company | | | | | | |
| Developed independently | 3.9** | (1.5) | −0.17 | (4.3) | 2.2 | (6.9) |
| Developed in alliance w/small licensee | −4.4 | (4.2) | 6.9 | (6.5) | −6.7 | (13) |
| Developed in alliance w/medium-size licensee | −9.2** | (4.8) | 17** | (3.8) | 8.6 | (9.6) |
| Developed in alliance w/large licensee | −1.6 | (4.0) | 13** | (4.6) | 7.1 | (8.8) |
| Indication originated by medium-size company | | | | | | |
| Developed independently | 3.6** | (1.6) | −3.1 | (4.1) | 0.87 | (6.5) |
| Developed in alliance w/small licensee | 5.2 | (3.7) | −4.0 | (9.7) | −6.7 | (14) |
| Developed in alliance w/medium-size licensee | 1.9 | (2.8) | −0.36 | (6.8) | 15** | (7.8) |
| Developed in alliance w/large licensee | −1.2 | (3.0) | 12** | (3.6) | 15** | (6.3) |
| Indication originated by large company | | | | | | |
| Developed independently | −3.0 | 1.0 | | | −0.73 | |
| Developed in an alliance | 2.9* | (1.6) | 2.2 | (3.8) | 11** | (4.7) |
| Number of indications for the compound | 2.6** | (0.33) | 3.2** | (0.64) | 4.3** | (1.0) |
| Screening Ratio | 4.9** | (2.4) | 27** | (5.8) | −0.65 | (9.3) |
| Observations | 2057 | | 1275 | | 861 | |
| $R^2$ | 0.06 | | 0.12 | | 0.13 | |
| Mean of the dependent variable | 88.2 | | 72.5 | | 61.2 | |

*Notes*: Dependent variable is one if an indication successfully completes the development stage, and zero otherwise. A small firm has 3 or fewer drugs in development during the sample period; a medium-sized firm has between 4 and 24, and a large firm has 25 or more. We include a full set of therapeutic category indicator variables in the regressions. The marginal effect is the change in the probability an indication will advance in clinical trials associated with a unit increase in the independent variable, holding the other regressors at their mean values, measured in percentage points. The marginal effect for large originators, which is the omitted group in the regression, is estimated by taking the difference from the predicted probability an indication will advance if originated by a large firm minus the predicted probability at the sample average of the regressors.

* Significantly different from zero at the 10% level.

** Significantly different from zero at the 5% level.

However, the insignificant marginal effects for small originators-small licensees and small originators-large licensees imply that this potential lemons or moral hazard problem does not apply to all alliances involving small originators. The drugs that small firms out-license to large firms and small firms do as well as the average of other drugs, but the drugs they out-license to medium-sized firms are less likely to complete phase 1. 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. 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 versus smaller licensees. For compounds originated by medium and large firms, out-licensing has no significant effect on phase 1 success rates.[19]

In phase 2 (column 3 of Table 5), indications that small firms out-license to medium-size and large firms have a 17 and 13 percentage point higher predicted probability of completing phase 2, respectively, than the average indication. Medium-size originators benefit from an alliance for phase 2 trials only when the licensee is a large firm. If a medium-size firm develops an indication with a large firm, the predicted probability of completing phase 2 is 12 percentage points higher than for the average indication.[20] 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 negative selection or moral hazard effects.

For phase 3, indications that medium-size firms develop in an alliance with a large firm have a 15 percentage point higher probability of successfully completing phase 3 than indications medium-size firms develop independently.[21] Likewise, indications that large firms develop in an alliance (with all size firms) have an 11 percentage point higher probability of succeeding than the average indication. 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%) of these that the small firms develop on their own. This small sample size makes the coefficient estimates 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.[22]

## 5. 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, the experience of the entire industry, 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

[19] In phase 1, for both small and medium-size originators the marginal effect of an alliance with a large licensee is not significantly larger than the marginal effect of an alliance with a small licensee.

[20] In phase 2, for a medium-size originator the marginal effect of an alliance is significantly greater if the licensee is large than if the licensee is small, whereas for small originators the difference in the marginal effects is not statistically significant.

[21] In phase 3, the marginal effect for a medium-size originator of an alliance with a large licensee is significantly larger than the marginal effect of an alliance with a small licensee, whereas for small originators the difference in the marginal effects is not statistically significant.

[22] The results in Table 5 are robust to excluding Screening ratio.

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 as an originator or licensee, does not appear to matter for phase 1 trials, which are small and relatively simple. However, for the larger and more complex phase 2 and phase 3 trials, there are positive returns to Total Experience up to a threshold. There is evidence of diseconomies of scope or breadth of experience in multiple therapeutic categories for phase 3 and no evidence of returns to category-specific experience in any phase. However, these returns to scale and scope are not robust to including firm fixed effects for the largest firms, which are jointly significant in phase 2 and phase 3. Phase 1 trials are more likely to succeed in therapeutic categories where the industry has considerable experience, which is consistent with knowledge spillovers for safety testing. The opposite is true for phase 2 and phase 3, however, which suggests that as a category becomes crowded, firms either must pursue more difficult phase 2 and phase 3 projects and/or the FDA raises approval standards. Finally, drugs developed by firms whose experience is focused rather than broad (diseconomies of scope) are more likely to complete phase 3 successfully.

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. This general finding that drugs developed in alliances are more likely to advance is consistent with DiMasi (2001) and Arora et al. (2000), but not Pisano (1997). 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 significant competitive entry into the market for pharmaceutical R&D, 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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