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Does Financing Have a Real Effect on Drug Development?

Andrew Metrick
The Wharton School
University of Pennsylvania and NBER

Sean Nicholson
Cornell University and NBER

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Abstract: We examine whether changes in financing availability affected the quantity and quality of drugs developed by biotech and pharmaceutical firms between 1989 and 2004. We find that financing does have a real effect on drug development, and this operates at both the aggregate and firm-specific levels. When it is relatively easy for U.S. firms to raise capital in a particular year, there is a relatively large amount of drug development activity in the subsequent two years. Firm specific access to financing also affects the quantity of drugs developed, but only in the relatively inexpensive preclinical stage. Aggregate and firm-specific financial constraints have opposite directional effects on the quality of drugs developed, as measured by the likelihood of advancing to the subsequent stage. Preclinical, Phase 1, Phase 2, and Phase 3 projects initiated when the capital markets are accessible are more likely to advance, whereas projects initiated when a firm is financially constrained are also more likely to advance. This is partially consistent with firms investing in projects of lower clinical quality when funds are plentiful, and vice versa when funds are scarce. Without information on the expected net present value of the projects initiated in periods of plentiful versus scarce capital, we cannot determine whether there is too much investment in the former case and/or too little investment in the latter case.

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Introduction

In this paper we examine whether changes in financing availability affected the quantity and quality of drugs developed by biotech and pharmaceutical firms between 1989 and 2004. Understanding whether and how financial constraints affect the biotech/pharmaceutical industry is important because these firms invest 19 percent of sales in research and development, which is almost twice the investment intensity of the second highest industry (PhRMA, 2005). One advantage to studying this industry is that we can observe the specific projects that biotech/pharmaceutical firms pursue rather than just a summary measure of the dollar amount invested in R&D. Specifically, we observe the date when drugs enter various development phases, the intended market for each drug, any firms that collaborate with the originating firm, and whether the project ultimately succeeds in reaching the market. Drugs of higher inherent quality will be more likely to complete each development stage, all else equal. Therefore we have good measures of the quantity of projects undertaken, the type of projects, and the quality of the projects.

A firm's demand for capital is derived by arranging potential investment projects in descending order based on each project's net present value. As a firm's cost of capital decreases, more projects will have a positive net present value (NPV) and the firm will demand more capital. In a perfectly-functioning capital market, firms will be able to raise unlimited amounts of capital at the appropriately risk-adjusted real interest rate, and will demand capital such that the marginal profitability of capital is equal to this rate. If capital markets function perfectly, financing should have no real effect on drug development. Companies will be able to obtain funding to develop projects (i.e., compounds) that have positive expected net present values using the risk-adjusted discount rate, but will not obtain funding for projects with a negative NPV.

Firms face financial constraints when the cost of external funds exceeds the cost of internal funds, and the greater is this wedge the more severe are the constraints (Kaplan and Zingales, 1997; Hubbard, 1998). In theory, the wedge could be created by information

asymmetries and/or agency problems; in practice, the wedge prevents a firm from borrowing or issuing equity at the risk-adjusted rate. That is, a firm under financial constraints will face a horizontal supply of capital up to a point, and then an upward sloping supply curve. If financial constraints are present and important in the biotech and pharmaceutical industry, then when financing is tight we would expect fewer projects to be initiated and the quality of the projects that are initiated to be relatively high. This would occur as firms move up the demand for capital curve and abandon relatively low-value projects.

Another possibility is that firms realize that financial constraints may have a real effect on drug development, and respond by raising more capital than needed for the short-term when the capital markets are receptive, such that they can ride out the dry period. Financing may affect the intensive as well as the extensive investment margin. When capital is relatively plentiful, it may be optimal for firms to spend more per project (e.g., enrolling more patients in a clinical trial or collecting data on multiple clinical outcomes). Additional spending could increase the probability that a drug successfully completes a phase, thereby offsetting the relatively low quality of the projects initiated in such periods. Access to financing may also affect whether firms that are co-developing a drug in an alliance commit as many resources to the project as intended.

There are a few studies that examine the consequences of financial constraints on biotech and pharmaceutical investment decisions. Lerner, Shane, and Tsai (2003) and Lerner and Merges (1998) find that in years when biotech companies raise relatively little public equity, these firms: 1) are more likely to form co-development alliances with partners; 2) transfer more property rights to the licensee firm; and 3) drugs developed under such alliances are less likely to reach the market. Vernon (2005) and Giaccotto, Santerre, and Vernon (2005) find that there is a relationship between the prices pharmaceutical firms receive and the amount they choose to invest, and part of this relationship is due to an increase in relatively low-cost internal funds.

We find that financing does have a real effect on drug development, and this operates at both the aggregate and firm-specific levels. When it is relatively easy and/or inexpensive for all U.S. firms to raise capital in a particular year, there is a relatively large amount of drug development activity in the subsequent two years. Specifically, a one-standard deviation increase in the aggregate liquidity index is associated with an average annual increase of 10.5 percent in the number of new trials initiated over the next two years. This relationship holds for preclinical activity, Phase 2 trials, and Phase 3 trials, but not Phase 1 trials. This pattern is consistent with comments made by biotech executives regarding how they respond to fluctuations in the availability of capital. Without information on the expected net present value of the projects initiated in periods of plentiful versus scarce capital, we cannot determine whether there is too much investment in the former case and/or too little investment in the latter case. Firm specific financial constraints, on the other hand, do not have a substantial impact on the quantity of drugs developed. By including firm fixed effects, we identify the effect of financing constraints at the firm level by changes in the degree of constraints over time within a firm.

Both aggregate and firm-specific financial constraints affect the quality of the drugs developed, where quality is measured by the likelihood of completing a development stage conditional on starting it. Preclinical, Phase 1, Phase 2, and Phase 3 projects initiated when capital markets are accessible are more likely to advance, all else equal. This is consistent with firms investing a relatively large amount per project when funds are plentiful. Firm-specific financial constraints have the opposite effect on project quality. That is, preclinical, Phase 1, and Phase 3 projects initiated during a period when a firm is experiencing financial constraints are more likely to advance to the next development stage, which is consistent with firms investing in projects of higher clinical quality when funds are scarce.

Data

We collect information on drugs in development from PharmaProjects, a data base assembled by Informa. Informa began recording the drug development activity of biotech and pharmaceutical companies in 1989. For every drug in development throughout the world, they attempt to record the company that originated the drug, any company involved in a co-development or licensing deal, the date of the licensing deal, the date the drug enters each development phase (i.e., preclinical, Phase 1, Phase 2, Phase 3, filing with a regulatory agency, and product launch), whether the drug was voluntarily terminated, and the therapeutic category the drug is targeting (e.g., cardiovascular disease, oncology). The data base contains information on a total of 22,929 drugs that were under development between 1989 and 2004, of which 11,401 were originated by companies that were public at some point between 1985 and 2003.¹ We focus in this paper on public companies that rely on capital markets to finance their R&D and therefore could be affected by financial constraints.²

In Figure 1 we present the number of drugs originated by publicly-traded companies that entered each of four development phases. The number of drugs entering preclinical testing, which is substantially larger than the number entering human trials, is reported at the bottom of Figure 1. The data for 2004 covers about one-half of the year because we obtained the PharmaProjects data set in July of 2004. The number of new preclinical drugs peaked in 1992, remained steady for several years, and then declined. Phase 1 and Phase 2 trials increased between 1989 and 2001 and then leveled off. Phase 3 trials have declined slightly since peaking in 1998.

As a proxy for the relative scarcity of capital, we use the liquidity index developed by Pastor and Stambaugh (2003). To construct this index, the authors measure the responsiveness of daily stock returns to volume shocks. Low responsiveness suggests that stock markets are

¹ Companies are included in our analysis if they have a GVKEY code, which is a unique company identifier in Compustat.

² Universities, non-profit research organizations, private companies, and foreign corporations that are not listed on U.S. stock market exchanges are excluded from our analysis.

sufficiently liquid to absorb the demand or supply shocks that drove high volume; high responsiveness suggests the opposite. Figure 2 plots this liquidity index. As shown in the figure, capital was relatively scarce in 1987, 1988, 1998, 2000, 2002, and 2003. In the empirical analysis we rescale the index so that all values are non-negative. That is, we add a constant amount to all years such that the index is zero when the index takes on its lowest value (2002). Our analysis tests the importance of this market-driven liquidity measure for real investment decisions at the firm level.

Financial information on publicly-traded companies is obtained from Compustat. For every year between 1987 and 2003, we collect a company's cash flow (earnings plus depreciation); the book value of its net property, plant and equipment (capital); Tobin's Q (market value of assets divided the book value of assets); long-term debt; dividends; and cash.

We derive a Kaplan-Zingales (KZ) index for each company and year based on coefficients from a regression conducted by Kaplan and Zingales and reported in Lamont, Polk, and Saa-Requejo (2001). Based on information from financial statements and annual reports, Kaplan and Zingales (1997) categorized 49 low-dividend manufacturing firms according to the degree to which they are having difficulty financing their investments. For example, firms that increased dividends or repurchased stock were deemed not to be financially constrained in that particular year, whereas firms that explicitly stated they were reducing investments due to liquidity problems were so classified. Kaplan and Zingales regress their categorical classification on five variables: the ratio of the firm's cash flow to book value of capital; Tobin's Q; the ratio of debt to capital; the ratio of dividends to capital; and the ratio of cash to capital. We apply the coefficients from this regression to each firm's relevant financial variables in year t to create a KZ index for each firm for every year between 1987 and 2003. Larger values of the KZ index correspond to greater financial constraint. For each year, we difference each firm's KZ index from the mean value for that year across all firms in the sample to remove any time trend component.

Ideally we would like the KZ index to accurately reflect the financial constraints facing firm j in year t and to be uncorrelated with unobserved measures of a firm's productivity and/or asset quality. One nice feature of the KZ index is that four of the five variables are drawn from accounting data, which are backward- rather than forward-looking. Tobin's Q is the only variable that has a market component – the market value of a firm's assets. Consider a company that has highly competent scientists and managers and drugs of unusually high quality. All else equal, this company will have a large market value of assets and a high Tobin's Q . The coefficient on this variable in the Kaplan and Zingales (1997) model is positive; this firm would have a relatively large KZ index and would appear to be more financially constrained than an otherwise similar firm. This may introduce some bias toward concluding that financial constraints today are associated with more future drug development activity and development of high-quality drugs. We minimize this concern by including company fixed effects in some specifications.

There are 570 public firms that developed a drug between 1989 and 2004 and are recorded in the PharmaProjects data set. We have the necessary financial data to derive a KZ index for 421 of these firms (74 percent) covering a total of 3,408 firm-years. Sample statistics for these firm-years are displayed in Table 1. The KZ index ranges substantially from -117 to 25. There are also considerable differences in the scale of R&D across the public firms in the sample. The median number of new preclinical, Phase 1, Phase 2, and Phase 3 drug trials initiated by a firm in a year is zero, although the observed maximums are much larger. The mean number of trials initiated by a firm each year is 1.98, 0.30, 0.28, and 0.16 for the four development phases, respectively.³

The public firms originated a total of 11,401 drugs that they developed independently or with one or more partner firms between 1989 and 2004. Six percent of these drugs are left

³ Following a merger or acquisition, PharmaProjects recodes the acquiring company as the originator of all drugs that were already developed, or were under development, by the acquired company. We use drug development data from a separate data set (NDA) to re-assign the originator as the acquired firm in years prior to the merger or acquisition.

censored; we do not observe the date when it entered preclinical testing. A drug is only included in the analysis when we observe the date it enters a development phase. A majority of the drugs are right-censored. For 8,548 of the 11,401 drugs (75 percent), for example, we observe the date it enters preclinical testing but have no further information on the drug's status. If a sufficient amount of time has elapsed since a drug entered a phase, we infer that the drug has been discontinued. We define failure thresholds for each phase using the sample of drugs where we observe the entry dates of two consecutive phases. Specifically, we set the failure threshold at the 95th percentile of the distribution for time elapsed in a phase for drugs that successfully completed that phase. The thresholds are five years (preclinical testing), four years (Phase 1), five years (Phase 2), and six years (Phase 3).

At the bottom of Table 1 we report sample statistics for drug trials that are not right-censored (after our failure threshold adjustment), have non-missing KZ index values for the originator firm, and have non-missing KZ index values for the firm that license the drug, where relevant. Only 19 percent of the drugs that enter preclinical testing advance to Phase 1. Success probabilities are higher for the clinical phases: 53 percent in Phase 1, 33 percent in Phase 2, and 42 percent in Phase 3. Drug development alliances are rare in preclinical testing but become more common during the more expensive development phases. Five percent of preclinical drugs are developed jointly by two or more companies versus 21 percent of Phase 3 trials. In all development stages except phase 3 the mean licensee KZ index is smaller than the mean KZ originator, which implies that access to capital may be one reason companies out-license their assets.

Method and Results

The first question we address is whether aggregate, all-industry capital scarcity affects the number of drugs that enter each of four development phases. An index of aggregate financial constraint is depicted in Figure 2. We regress the number of preclinical, Phase 1, Phase 2, and

Phase 3 trials initiated by all public biotech and pharmaceutical firms in year t on a time trend and the aggregate liquidity index for year $t-1$ and year $t-2$. We include two lags because it takes time for firms to obtain regulatory approval to conduct a trial and then to recruit physicians and patients. In order to pool observations across phases and to compare the magnitude of coefficients between the phase-specific regressions, we define the dependent variable as the ratio of trials for a particular phase initiated in year t relative to the number initiated in 1999, which is a fairly representative year (see Figure 1).

Regression results are reported in Table 2, pooled for all phases in column one and then separately by phase in the remaining columns. The positive time trend coefficient in all five specifications confirms that aggregate development activity increased over the 1989 to 2004 time period. In the pooled specification both aggregate liquidity coefficients are positive and significant. When capital is plentiful/inexpensive for biotech and pharmaceutical firms (and all other firms) in a particular year, there is a relatively large amount of drug development activity in the subsequent two years. Specifically, a one-standard deviation increase in the aggregate liquidity index is associated with an average annual increase of 10.5 percent in the number of new trials initiated over the next two years. Without information on the expected net present value of the projects, we cannot determine whether there is too little investment when capital is tight or too much when capital is plentiful. However, at the aggregate level there is clearly an association between financing and drug development investment activity.

Phase-specific regressions are reported in the next four columns of Table 2. The aggregate liquidity variables are jointly significant in all but the Phase 1 regression, and the magnitudes are largest in Phase 3 regression. One explanation for these results is that Phase 1 is the most heavily regulated phase. Companies must file an investigational new drug (IND) application with the Food and Drug Administration (FDA) before initiating safety testing on humans in Phase 1, whereas the decision to initiate Phase 2 and Phase 3 trials are unilateral. Once companies receive an IND approval, they may be reluctant to terminate or postpone Phase 1

trials even if public equity becomes expensive.⁴ Preclinical research is much less expensive than running human clinical trials, and therefore one may expect them to be less sensitive to changes in financial constraints. However, the large positive coefficients in the second column of Table 2 are consistent with comments from executives at biotech firms that when the window to the capital market closes, companies divert resources from early-stage research and focus on their late-stage product(s).⁵ Phase 3 is the most expensive development stage. Firms may postpone the initiation of a Phase 2 trial until they are assured they have enough funding to complete the multi-year phase.

Our finding that aggregate liquidity affect biotech/pharmaceutical investment activity will be more convincing if we find effects at the company level in addition to the aggregate level. That is, when a firm experiences relatively (to its average) severe financial constraints, does it subsequently initiate fewer trials than average? We estimate four phase-specific regressions of the following form, where a unit of observation is the number of drugs originated by company j that enter phase k in year t :

$$(1) N_{jkt} = \beta_1 \text{KZ_index}_{j,t-1} + \beta_2 \text{KZ_index}_{j,t-2} + \beta_3 \text{Aggregate liquidity}_t + \beta_4 \text{Aggregate liquidity}_{t-1} + \beta_5 \text{Aggregate liquidity}_{t-2} + \varepsilon_{jkt}$$

We estimate equation (1) with a negative binomial regression. Companies with robust pipelines and competent personnel should be able to attract more capital, which implies there should be a negative correlation between a company's KZ index and its R&D output in the cross-section (recall that higher values of the KZ index correspond to greater degrees of financial constraint). Indeed, mean annual output for company-years with a KZ index below the median value are two to three times larger across the four development phases than company-years with a KZ index above the median value. By including fixed effects, β_1 and β_2 are identified by variations over time in a company's financial constraints.

⁴ This would especially be true for firms that expect to interact repeatedly with the FDA.

⁵ Based on conversations with Kevin Buchi of Cephalon, Stephen Mueller of Encysive, and Paul Van Damme of Lorus Therapeutics in the fall of 2005.

Coefficient estimates from four separate phase-specific regressions of equation (1) are reported in Table 3. The coefficients are exponentiated and therefore are interpreted as incidence rate ratios. Coefficients greater than one indicate that an increase in the regressor is associated with an increase in the rate at which a company initiates drug development in that phase, and conversely for coefficients less than one. As in the industry-wide analysis, the aggregate liquidity coefficients are positive and jointly significant in all development stages except Phase 1, and the largest effect occurs in Phase 3. Specifically, a one-standard deviation (0.365) increase in the aggregate liquidity index is associated with a 10 percent, eight percent, and 14 percent increase in the number of preclinical, phase 2, and phase 3 trials initiated per year over the next three years, respectively. The two lagged company-specific financial constraint coefficients are not significant in any of the four regressions reported in Table 3.

In Table 4 we report the results of regressions where we interact a company's KZ index in a particular year with the aggregate liquidity index for that year. Our objective is to see whether company-specific financial constraints have a larger effect on the number of new trials started when capital markets are tight. Consider the first two coefficients reported in the preclinical regression. When the market had the least amount of liquidity (2002), the aggregate liquidity index had a value of zero, so the interaction of KZ_{t-1} and the aggregate liquidity index would also be zero. The coefficient on a company's lagged KZ index is significantly greater than one. This indicates that when a firm is financially constrained (i.e., the firm has a relatively large/positive KZ index), it will start a relatively large number of preclinical trials in the subsequent year. At the mean value of aggregate liquidity (0.78), however, financial constraints do not have an impact on preclinical starts.

This result is surprising. One explanation is that managers "open the floodgates" out of desperation in order to make the company's pipeline appear robust enough to raise funds in a tight capital market. The coefficients on the first and second lags of the KZ index are insignificant for Phase 1, Phase 2, and Phase 3. Access to financing appears to have a real effect

on investment at the firm level, but only in relatively inexpensive early-stage projects. Again, this is consistent with statements from biotech managers that resources get focused on late-stage projects when financing is expensive.

Our final question is whether firms that are financially constrained decide to develop their relatively high-quality drugs, where quality is measured as the likelihood a drug will successfully completing a development stage conditional on starting it. This would offer further evidence that firms work their way down the marginal efficiency of investment schedule according to how much capital is available.

The unit of observation for this analysis is a drug trial, and the dependent variable is one if the drug enters the next development phase or, in the case of starting Phase 3, if the drug is approved in a major market (the United States, the European Union, or Japan). We run four separate stage-specific logistic regressions of the following form:

$$(2) \text{ Complete stage | starting stage in year } t = \beta_1 + \beta_2 \text{KZ_orig_t-1} + \beta_3 \text{KZ_orig_t-2} + \beta_4 \text{Licensed} + \beta_5 \text{KZ_orig_lic_t-1} + \beta_6 \text{KZ_orig_lic_t-2} + \beta_7 \text{KZ_lic_t-1} + \beta_8 \text{KZ_lic_t-2} + \beta_9 \text{AG_index_t} + \beta_{10} \text{AG_index_t-1} + \beta_{11} \text{AG_index_t-2} + \beta_{12} \text{TC}$$

Positive β_2 and β_3 coefficients would be consistent with the hypothesis that firms focus their resources on high-quality drugs when they are financially constrained. Our measure of drug quality is based on both the inherent attributes of the compound and decisions made by the firm.

For drugs that are licensed before the beginning of a development stage, we include two separate variables to measure financial constraints for the originator (the two KZ_orig_lic variables), and two variables to measure financial constraints facing the licensee (the two KZ_lic variables). We include three separate sets of financial constraint variables to allow the effect for an originator firm to differ depending on whether it is developing a drug independently or with another company, and to allow the effect of an originator firm's constraints to differ from the licensee firm's constraints in co-developed projects.

We present regression results for four logistic regressions in Table 5. The three aggregate liquidity coefficients are positive and jointly significant for all four development stages. Projects initiated when capital is plentiful (and in the subsequent two years) are more likely to advance, all else equal. This is surprising; we expected firms would invest in projects of lower clinical quality when funds were plentiful. The magnitudes of these coefficients are large. A one-standard deviation increase in aggregate liquidity (0.75) in $t-1$ is predicted to increase the probability that a drug entering preclinical testing in year t will advance to Phase 1 by 4.3 percentage points (22.5 percent). The predicted increases in the survival probabilities for Phase 1 (36.0 percent), Phase 2 (69.8), and Phase 3 (95.2) for a similar change in aggregate liquidity are even larger. One explanation for these results is that firms may spend more per trial when the capital markets are accessible, and this increased spending increases the ultimate survival probabilities, even if the marginal drug candidate entering a stage is of lower inherent quality.

The coefficients on the originating firm's financial constraint variables are positive and jointly significant for preclinical testing, Phase 1, and Phase 3. In those phases, projects initiated in the two years after a firm experienced financial constraints are more likely to advance to the next development stage. This is consistent with firms choosing to focus resources on their high-quality projects, defined as those that are likely to advance to the subsequent stage. The magnitudes of these coefficients are smaller than the aggregate liquidity effect. A one-standard deviation increase in a firm's KZ index in year $t-1$ (a worsening of financial constraints) is associated with an increase of 1.8 percentage points (9.3 percent) in the probability a drug that enters preclinical testing in year t will advance to Phase 1, and an increase of 7.0 percentage points (13.1 percent) in the probability a Phase 1 drug will successfully complete that phase. For Phase 3, the marginal effect of a worsening of financial constraints in year $t-2$ is 7.4 percentage points (17.8 percent). We find, therefore, that changes in aggregate liquidity and changes in company-specific financial constraints have opposite effects on the quality of drug candidates.

In the preclinical regression, the licensing firm's financial constraints affect the likelihood the co-developed drug will advance to Phase 1. Specifically, drugs that enter preclinical testing in year t are less likely to advance when the licensee was facing relatively severe financial constraints in year $t-1$. This could occur if the licensee is unable to deliver as many resources to the project as specified in the contract. A similar effect occurs in the Phase 2 regression, where a licensee's financial constraints in year $t-2$ reduce the likelihood a drug that enters Phase 2 in year t will advance to Phase 3. Financial constraints have the same effect in Phase 2 for the firm that originated the drug. It appears, therefore, that financial constraints have a different effect for drugs being developed in alliances than drugs developed independently by the originator.

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Table 1

Sample Statistics

Panel A: Firm-year Observations (n = 2,897)

	<u>Minimum</u>	<u>Median</u>	<u>Maximum</u>	<u>Mean</u>	<u>Standard Deviation</u>
KZ Index	-117	0.41	24.6	0.15	3.91
Aggregate liquidity	0.00	0.89	1.21	0.73	0.37
New trial starts in year t:					
- Preclinical	0	0	85	1.98	5.84
- Phase 1	0	0	10	0.30	0.78
- Phase 2	0	0	9	0.28	0.78
- Phase 3	0	0	7	0.16	0.51

Panel B: Means of Drug Trial Observations

	<u>Preclinical</u> (n = 5,123)	<u>Phase 1</u> (n = 771)	<u>Phase 2</u> (n = 711)	<u>Phase 3</u> (n = 408)
Proportion completing phase	0.193	0.533	0.333	0.415
Originator's KZ index	-1.14	-0.768	-0.706	-0.487
Aggregate liquidity	0.775	0.730	0.750	0.749
Co-development alliance	0.050	0.127	0.121	0.211
For co-developed drugs:				
- Originator's KZ index	-0.010	0.009	-0.017	-0.277
- Licensee's KZ index	-0.037	-0.103	-0.169	-0.238

Table 2

Industry Aggregate New Drug Trials, 1989 – 2004

<u>Variable</u>	<u>All Phases Pooled</u>	<u>Preclinical</u>	<u>Phase 1</u>	<u>Phase 2</u>	<u>Phase 3</u>
Time trend	0.037** (0.0042)	0.023** (0.0056)	0.039** (0.0075)	0.031** (0.0048)	0.056** (0.012)
Aggregate liquidity, t-1	0.214** (0.074)	0.211* (0.090)	0.011 (0.107)	0.040 (0.041)	0.595** (0.194)
Aggregate liquidity, t-2	0.360** (0.055)	0.476** (0.069)	0.117 (0.087)	0.299** (0.064)	0.548** (0.154)
Constant	0.934** (0.0359)	1.18** (0.061)	0.791** (0.063)	0.780** (0.046)	0.988** (0.082)
Observations	64	16	16	16	16
R ²	0.44	0.73	0.71	0.79	0.63
F-test on the joint significance of the liquidity measures	0.000	0.000	0.414	0.002	0.001

Notes: Dependent variable is the number of new drug trials initiated by all public biotech/pharmaceutical firms in year t divided by the number initiated in 1999. ** = significantly different from zero at the 5-percent level. * = significantly different from zero at the 10-percent level.

Table 3

Coefficient Estimates from (Company) Fixed-Effect Negative Binomial Regressions

<u>Variable</u>	<u>Preclinical</u>	<u>Phase 1</u>	<u>Phase 2</u>	<u>Phase 3</u>
Company's KZ index, t-1	1.00	0.988	0.994	0.999
Company's KZ index, t-2	0.997	0.995	0.986	1.01
Aggregate liquidity, t	1.19**	1.17	1.12	1.06
Aggregate liquidity, t-1	1.37**	1.29**	1.35**	1.58**
Aggregate liquidity, t-2	1.29**	1.04	1.22	1.50**
Observations	2,665	1,856	1,872	1,659
P-value on joint significance of KZ index variables	0.906	0.741	0.584	0.943
P-value on joint significance of aggregate liquidity variables	0.000	0.138	0.046	0.005

Notes: The dependent variable is the number of new drug trials initiated by company j in year t . Coefficients are exponentiated to represent incidence rate ratios. ** = significantly different from zero at the 5-percent level. * = significantly different from zero at the 10-percent level. Although there is complete financial information for 2,897 firm-years, the number of observations in each regression is lower because firms that never initiated a trial for a particular phase are omitted from the fixed-effect negative binomial regression.

Table 4

Coefficient Estimates from (Company) Fixed-Effect Negative Binomial Regressions, With Interaction Terms

<u>Variable</u>	<u>Preclinical</u>	<u>Phase 1</u>	<u>Phase 2</u>	<u>Phase 3</u>
Company's KZ index, t-1	1.06**	1.06	1.01	1.08
KZ, t-1 * Aggregate liquidity, t-1	0.929**	0.915**	0.979	0.903*
Company's KZ index, t-2	0.968	0.940	0.942	1.01
KZ, t-2 * Aggregate liquidity, t-2	1.03	1.07	1.05	0.982
Aggregate liquidity, t	1.24**	1.23*	1.15	1.06
Aggregate liquidity, t-1	1.39**	1.29**	1.35**	1.56**
Aggregate liquidity, t-2	1.27**	1.03	1.22	1.47**
Observations	2,665	1,856	1,872	1,659

Notes: The dependent variable is the number of new drug trials initiated by company j in year t . Coefficients are exponentiated to represent incidence rate ratios. ** = significantly different from zero at the 5-percent level. * = significantly different from zero at the 10-percent level. Although there is complete financial information for 2,897 firm-years, the number of observations in each regression is lower because firms that never initiated a trial for a particular phase are omitted from the fixed-effect negative binomial regression.

Table 5

Coefficient Estimates of the Probability of Completing a Phase Conditional on Starting It

<u>Variable</u>	<u>Preclinical</u>	<u>Phase 1</u>	<u>Phase 2</u>	<u>Phase 3</u>
Originator's KZ index, t-1	0.047** (0.019)	0.126** (0.041)	0.012 (0.047)	-0.104 (0.084)
Originator's KZ index, t-2	0.051** (0.019)	0.025 (0.034)	0.026 (0.040)	0.193** (0.085)
Aggregate liquidity, t	0.617** (0.132)	0.829** (0.259)	0.743** (0.295)	1.214** (0.397)
Aggregate liquidity, t-1	0.408** (0.108)	1.041** (0.226)	1.446** (0.269)	2.274** (0.418)
Aggregate liquidity, t-2	-0.283* (0.152)	0.185 (0.299)	0.426 (0.353)	0.925* (0.518)
Co-development alliance	0.785** (0.166)	0.453* (0.268)	0.427 (0.330)	0.503 (0.377)
Constant	-3.16** (0.352)	-1.77** (0.728)	-2.99** (0.912)	-3.22** (1.12)
For co-developed drugs:				
Originator's KZ index, t-1	0.051 (0.075)	0.123 (0.115)	-0.363** (0.164)	0.058 (0.078)
Originator's KZ index, t-2	-0.020 (0.084)	0.002 (0.152)	0.094 (0.136)	-0.100 (0.112)
Licensee's KZ index, t-1	-0.199** (0.087)	-0.145 (0.150)	0.094 (0.145)	0.535 (0.342)
Licensee's KZ index, t-2	0.082 (0.094)	0.302* (0.175)	-0.334** (0.151)	-0.490 (0.339)
Constant	-3.16** (0.352)	-1.77** (0.728)	-2.99** (0.912)	-3.22** (1.12)
Observations	5,123	771	711	408
Pseudo-R ²	0.05	0.06	0.11	0.19
P-value on originator KZ variables:				
- independently developed drug	0.000	0.001	0.729	0.074
- co-developed drug	0.540	0.597	0.076	0.487
P-value on licensee KZ variables	0.056	0.305	0.122	0.292
P-value on aggregate liquidity variables	0.000	0.000	0.000	0.000

Notes: Dependent variable is one if a drug successfully completed a phase that was initiated in year t, and is zero otherwise. Right-censored drug trials are not included. A full set of therapeutic category indicator variables (e.g., cancer) are included. ** = significantly different from zero at the 5-percent level. * = significantly different from zero at the 10-percent level.

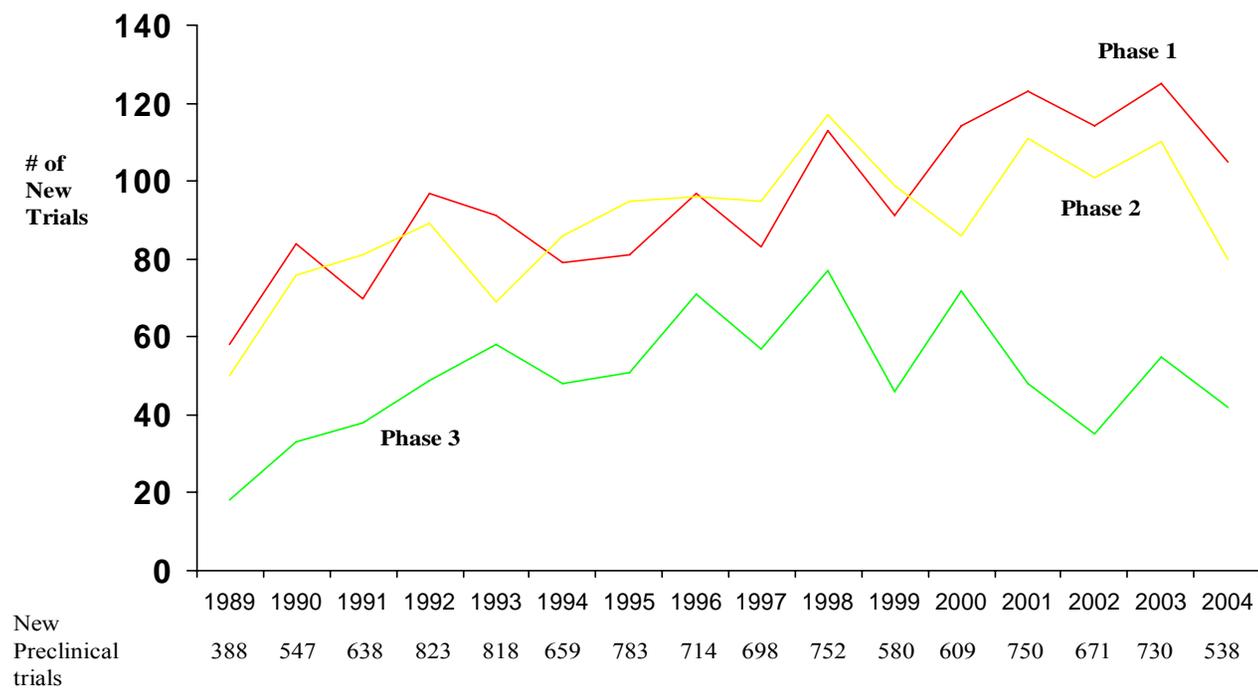
Figure 1**New Clinical Trials Initiated by Public Companies, 1989 – 2004**

Figure 2

Aggregate, All Industry U.S. Liquidity Measure, 1985 - 2003

