

Can a Liquid Market Save Your Life?

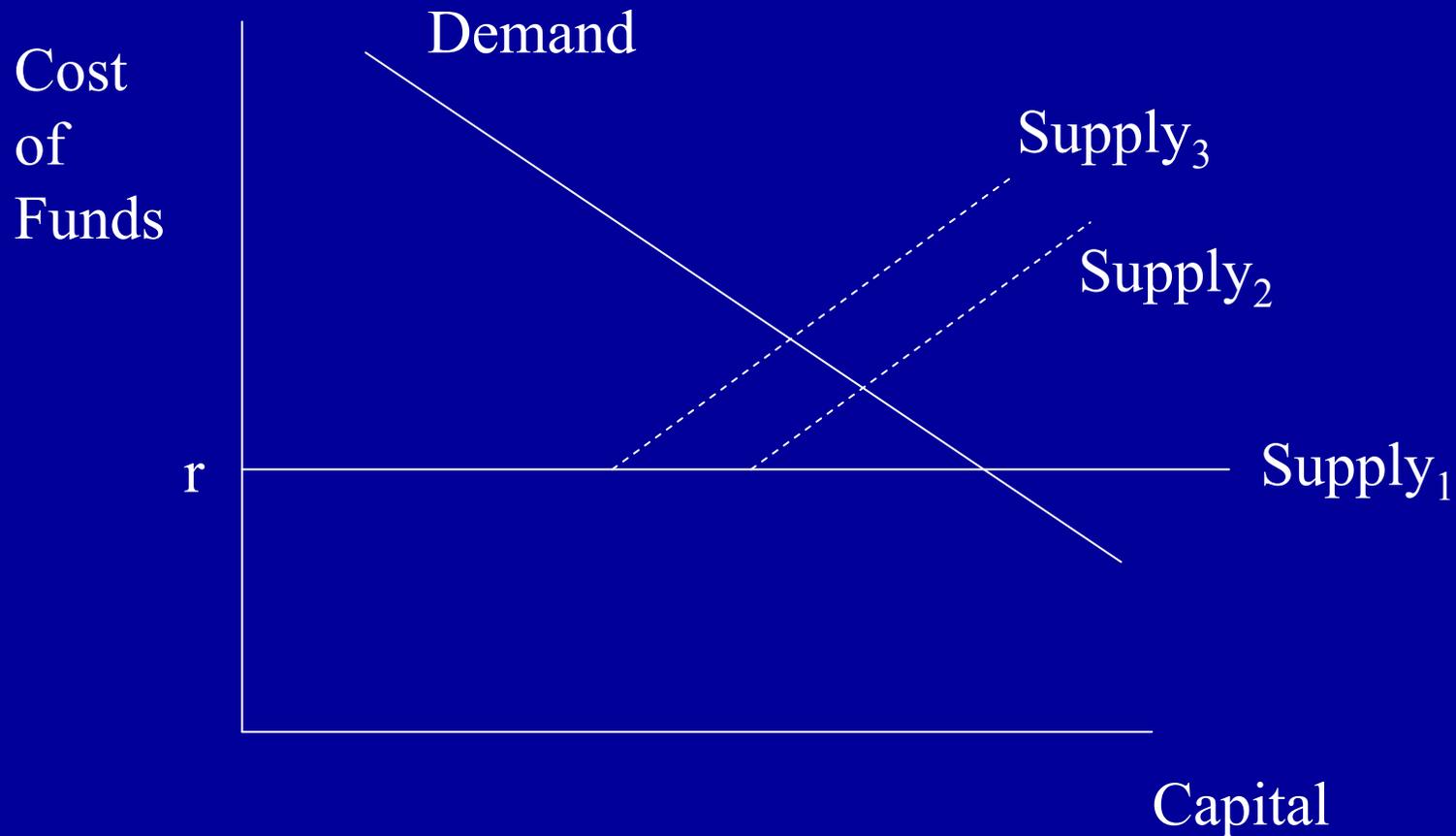
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Introduction

- Biotech and pharmaceutical firms invest higher % of sales in R&D (19%) than any other industry.
- New technologies are the catalyst behind increases in health care costs (and benefits?).
- If capital markets function perfectly, financing should have no affect on quantity or quality of drugs developed.
- Research question: does access to capital affect the quantity and/or quality of drugs developed? Do the capital effects operate at the market-wide and/or company-specific level?

A Firm is Financially Constrained if There is a Wedge Between the Internal and External Cost of Funds



Source: Hubbard (1998).

How Financial Constraints Should Affect a Firm's Drug Development

Standard prediction:

- initiate fewer projects
- funded projects have relative high NPV

Other considerations

- “Rainy Day Fund”
- Regulatory constraints may prevent adjustment on the extensive margin (i.e., delay), so adjustment occurs on intensive margin (e.g., spend less per project).
- Alliances and incomplete contracts: constrained firm may commit fewer resources than promised.

Biotech Companies Took Full Advantage of the “Open Window” in 2000

U.S. Biotech Fundraising (\$millions)

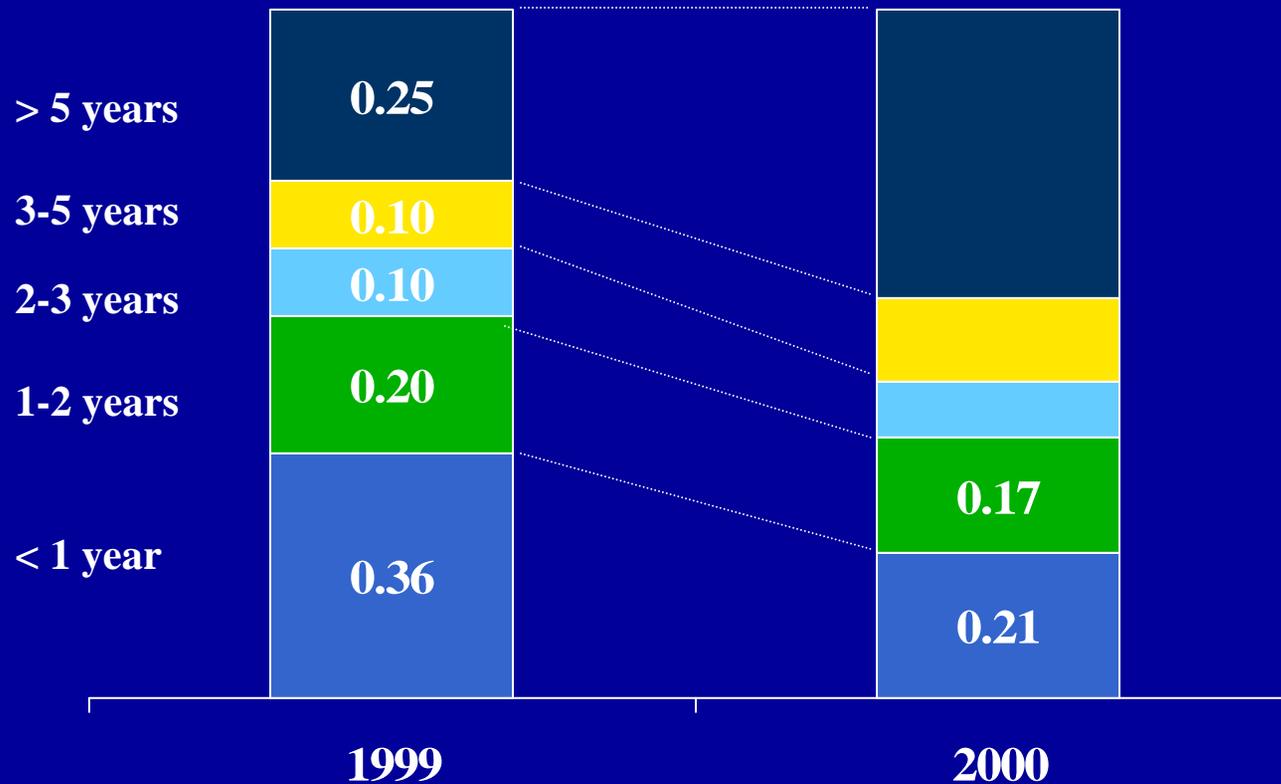
Source as % of total
funding, 1997-2002



Source: Burrill & Company.

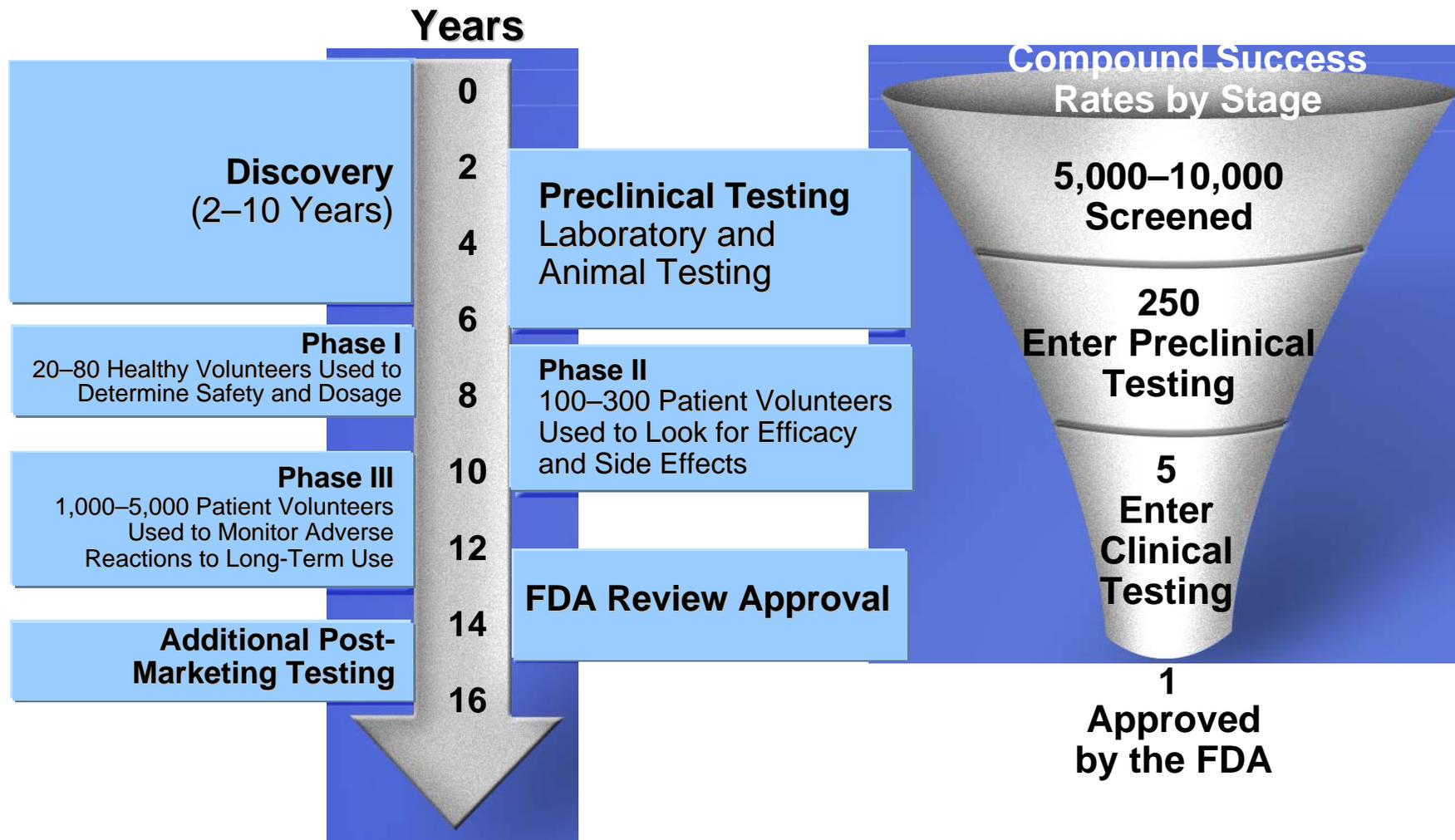
Financing Boom Strengthened Biotech Balance Sheets

Percent of Biotech Companies According to Years of Cash Available
(at current burn rate)



Source: financial statements, Ernst & Young, and CMS report.

New Product Development – A Risky and Expensive Proposition

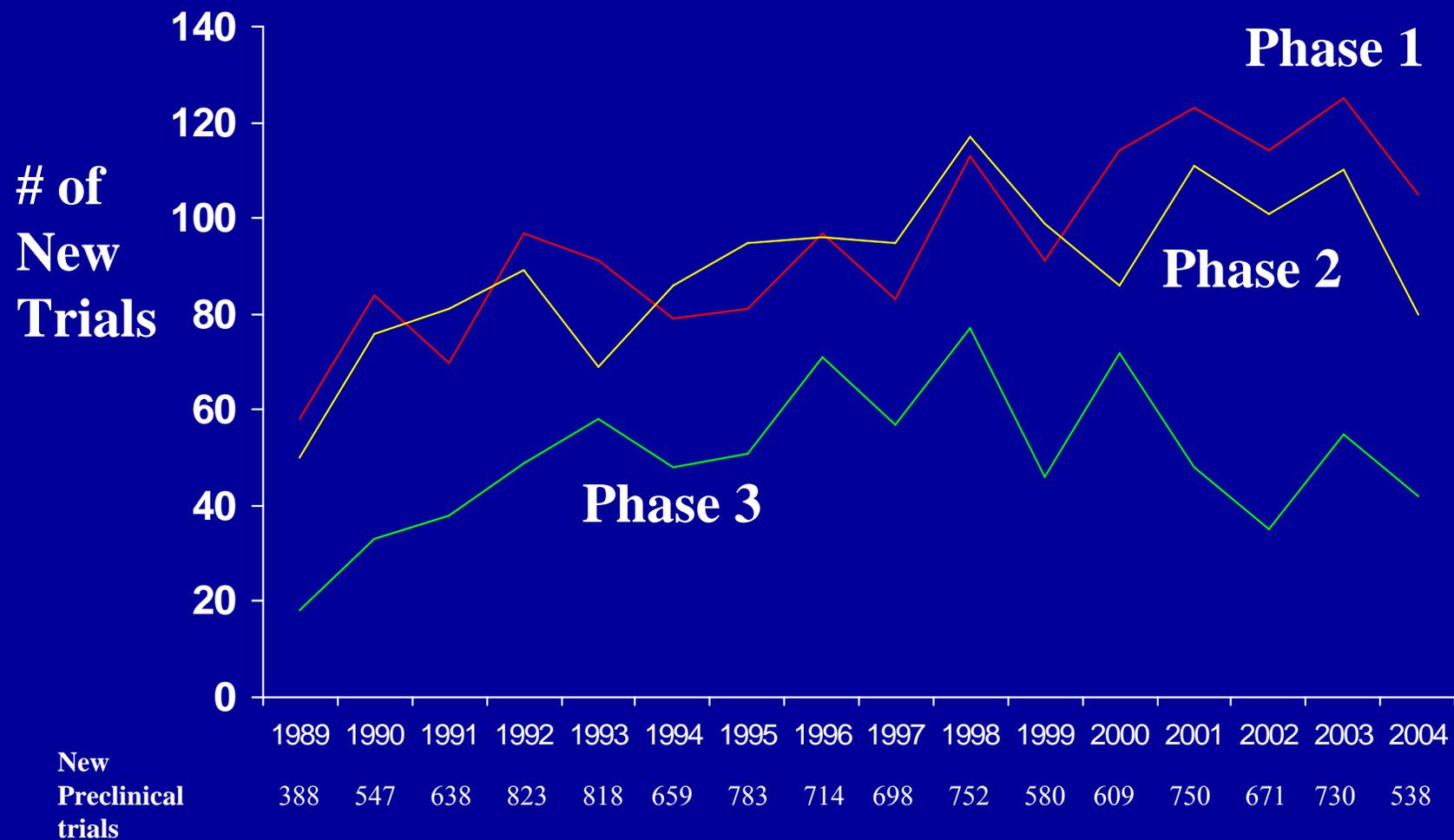


Source: PhRMA Pharmaceutical Industry Profile 2003, Chapter 1: Increased Length and Complexity of the Research and Development Process. DiMasi, JA, Hansen, RW, Grabowski, HG. "The Price of Innovation: new estimates of drug development costs." *J Health Economics*. 2003;22:151-185.

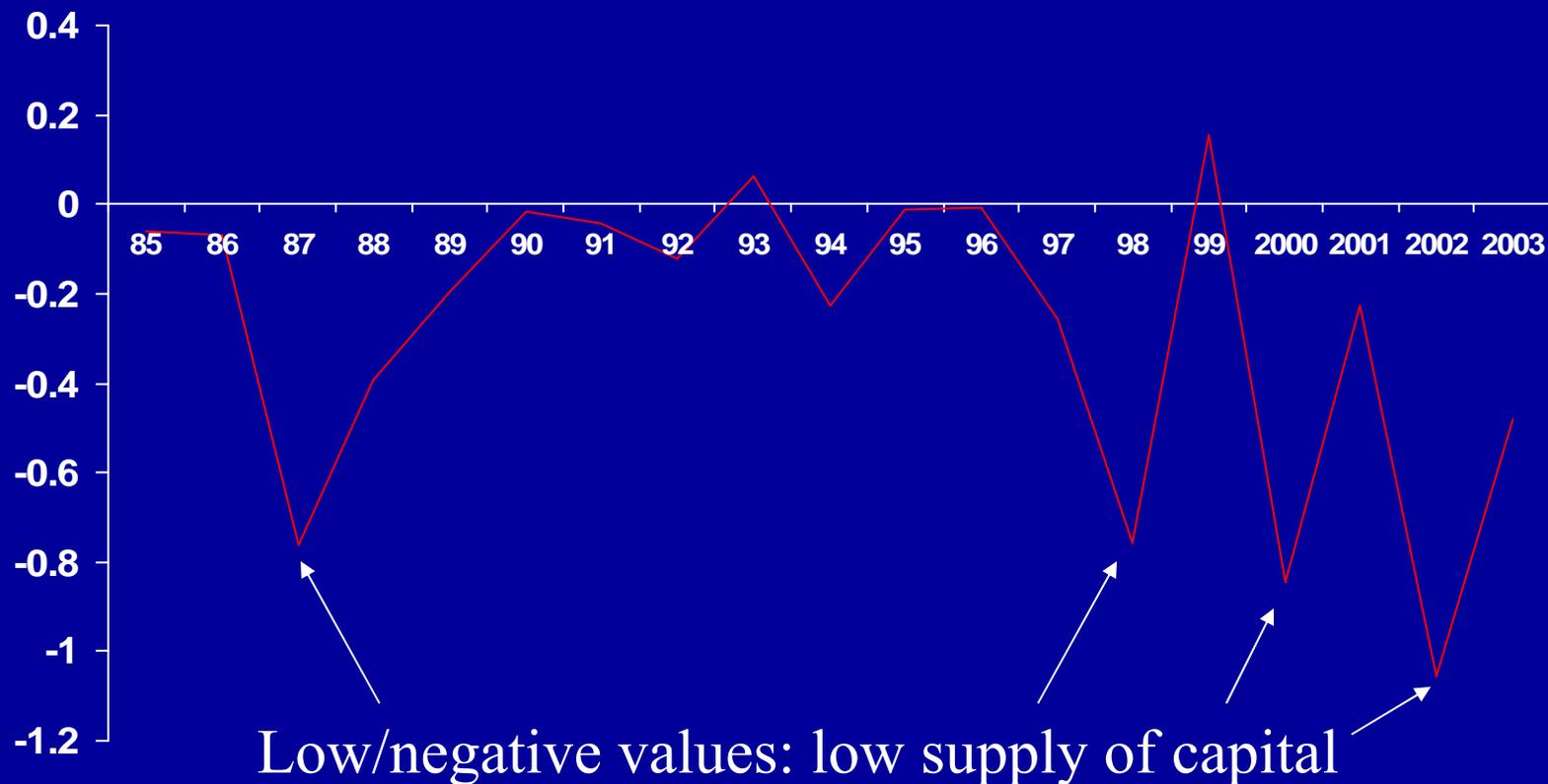
Description of Data

- PharmaProjects: 11,401 drugs originated by public companies and under development btwn 1989 and 2004:
 - date drug begins each development phase and is approved
 - firm(s) co-developing drug, and date of agreement
 - therapeutic category (e.g., oncology)
- Aggregate liquidity index (Pastor and Stambaugh, 2003): responsiveness of daily stock returns to volume shocks.
- Firm-specific financial constraints. Derive a KZ (Kaplan and Zingales, 1997) index for each firm-year by applying their regression coefficients to a firm's accounting and market data:
 - Cash flow/Book value of capital (-)
 - Market value of assets/Book value of assets (+)
 - Debt/Capital (+)
 - Dividends/Capital (-)
 - Cash/Capital (-)

New Clinical Trials Initiated by Public Companies 1989 – 2004



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



Liquidity index is re-scaled to have a minimum value of 0.

Question 1: Does aggregate liquidity affect the quantity of drugs developed?

$$N_{kt} = \alpha_1 \text{Time Trend} + \alpha_2 \text{Aggregate Liquidity Index}_{t-1} + \alpha_3 \text{Aggregate Liquidity Index}_{t-2} + \varepsilon_{jt}$$

Dependent variable: ratio of drugs that entered phase k in year t relative to the number of drugs that entered phase k in 1999.

We pool Preclinical, Phase 1, Phase 2, and Phase 3 as well as estimating each development stage separately.

Aggregate Regression Results

<u>Variable</u>	All Phases				
	<u>Pooled</u>	<u>Preclinical</u>	<u>Phase 1</u>	<u>Phase 2</u>	<u>Phase 3</u>
Time trend	0.037**	0.023**	0.039**	0.031**	0.056**
Aggregate liquidity, t-1	0.214**	0.211*	0.011	0.040	0.595**
Aggregate liquidity, t-2	0.360**	0.476**	0.117	0.299**	0.548**
Constant	0.934**	1.18**	0.791**	0.780**	0.988**
Observations	64	16	16	16	16
R ²	0.44	0.73	0.71	0.79	0.63
F-test on joint significance of the liquidity measures	0.000	0.000	0.414	0.002	0.001

Question 2: Do firm-specific financial constraints affect the quantity of drugs developed?

$$N_{jkt} = \beta_1 \text{KZ_index}_{j,t-1} + \beta_2 \text{KZ_index}_{j,t-2} + \beta_3 \text{Aggregate Liquidity}_t + \beta_4 \text{Aggregate Liquidity}_{t-1} + \beta_5 \text{Aggregate Liquidity}_{t-2} + \beta_6 \text{Time Trend} + \varepsilon_{jkt}$$

Dependent variable: # of drugs originated by company j that enter phase k in year t.

Estimate a negative binomial regression with firm fixed effects.

Median Number of Drug Starts Per Year is Zero

Development <u>Stage</u>	<u>Median</u>	<u>Mean</u>	<u>Max</u>	<u>Completion Probability</u>
Preclinical	0	1.98	82	0.19
Phase 1	0	0.30	9	0.53
Phase 2	0	0.28	9	0.33
Phase 3	0	0.16	7	0.41

Firm-Year Regression Results (Incident Rate Ratios)

<u>Variable</u>	<u>Preclinical</u>	<u>Phase 1</u>	<u>Phase 2</u>	<u>Phase 3</u>
KZ, t-1	0.698**	1.01	0.859	0.719
KZ, t-2	0.876	0.913	0.934	0.654
Aggregate liquidity, t	0.793**	0.782	0.856	0.759
Aggregate liquidity, t-1	1.01	0.976	1.07	1.42*
Aggregate liquidity, t-2	1.40**	1.16	1.33**	1.67**
Time trend	0.972**	0.978	0.982	1.01
Observations	2,378	1,657	1,785	1,488
P-value on joint significance of KZ variables	0.004	0.925	0.730	0.167
P-value on joint sig. of aggregate liquidity variables	0.000	0.171	0.100	0.003

Summary of Firm-Year Regression Results

- A 1-standard deviation increase in Aggregate Liquidity in year t is associated with an average annual increase in the number of new trials started over next 3 years:
 - Preclinical: 7%
 - Phase 1: no effect
 - Phase 2: 3%
 - Phase 3: 10%
- A one-standard deviation decrease (improvement) in a firm's financial constraints is associated with a 6% increase in new preclinical testing per year over the subsequent two years relative to the firm's average number of starts.

Question 3: do financial constraints affect the quality of the drugs that are developed?

- Unit of observation: a drug trial.
- Dependent variable: 1 if a drug completes a stage, conditional on starting it, and zero otherwise.
- Left censoring: only include drugs if we observe the date the drug entered that stage.
- Right censoring: we assume a drug has failed if it spends more than 4 yrs in Ph 1; 5 yrs in Pre-clinical or Ph 2; 6 yrs in Ph 3. Other right-censored drugs are omitted.
- Estimate 4 stage-specific logistic regressions.
- Include originator's KZ index in years $t-1$ and $t-2$; and licensee's KZ index for drugs being co-developed.
- Aggregate liquidity index and therapeutic category indicators also included.

Median Number of Drug Starts Per Year is Zero

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Summary of Drug-Quality Regression Results

- A 1-standard deviation decrease (improvement) in a firm's financial constraints in t-2 is associated with lower survival probabilities for projects initiated in year t:
 - 10% for Preclinical testing (1.9 percentage points)
 - 13% for Phase 1 (6.7 percentage points)
- Similar result in logit with firm fixed effects
- 1-standard deviation increase in Aggregate Liquidity in year t-1 is associated with higher survival probabilities of projects initiated in year t:
 - 7% for Preclinical testing
 - 17% for Phase 1
 - 34% for Phase 2
 - 37% for Phase 3

Effect of Financing on Drugs Developed in An Alliance of 2 or More Companies

- **Phase 1:** co-developed drugs entering Phase 1 in year t more likely to advance to Phase 2 if either the originating firm or the licensing firm were facing financial constraints in year $t-1$ or year $t-2$.
- Consistent with firms focusing resources on highest quality projects when capital is scarce.
- Result holds in fixed effects logit.

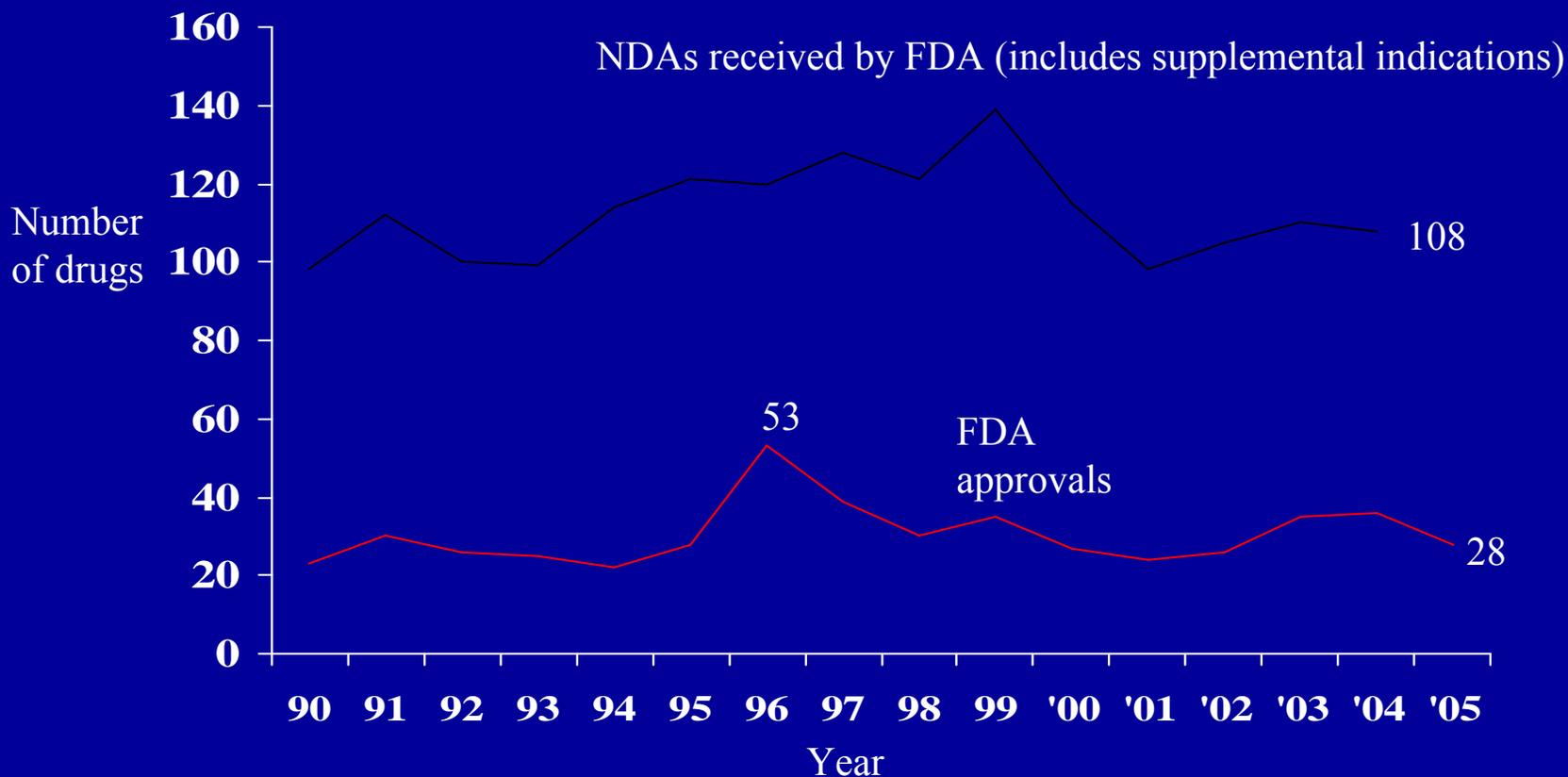
Conclusions

- Financing has a real effect on both the quantity and quality of drugs developed.
- When capital is relatively plentiful, firms develop more drugs and those drugs are more likely to advance.
- Firms facing few financial constraints develop more preclinical drugs, and their preclinical and Phase 1 drugs are less likely to advance.
- Aggregate liquidity has a stronger effect, and may be swamping effect of firm-specific financial constraints.
- Need information on the expected net present value of projects initiated in periods of plentiful vs. scarce capital to determine whether there is too much investment when capital is plentiful or too little when capital is scarce.
- Plan to focus on oncology next.

EXTRA SLIDE

Pharmaceutical R&D Output is Flat

Number of NDAs Received by FDA and NMEs Approved by FDA, 1990-2005



Source: Food and Drug Administration (FDA).

Note: NME = new molecular entity; NDA = new drug application received by FDA.