Does Public Scientific Research Complement Private Investment in Research and Development in the Pharmaceutical Industry?

Andrew A. Toole *Rutgers University*

Abstract

This paper analyzes how pharmaceutical research and development (R&D) investment responds to publicly supported biomedical research performed mainly at universities and nonprofit institutions. New microlevel data on investment, by the U.S. National Institutes of Health, allow measures of public basic and clinical research in seven medical classes to be included in a distributed lag model explaining pharmaceutical R&D investment. Using a panel of medical classes observed over 18 years, the analysis found strong evidence that public basic and clinical research are complementary to pharmaceutical R&D investment and thereby stimulate private-industry investment. However, differences in the relevance and degree of scientific and market uncertainty between basic and clinical research lead to differences in the magnitude and timing of the pharmaceutical investment response.

1. Introduction

Policymakers in the United States and abroad are engaged in an ongoing debate about the proper role of government in the development of scientific and technical knowledge. The debate centers on how much public money should be spent on scientific research and on which areas of research should receive funding. Policymakers who support public funding believe this research creates knowledge that complements private-industry investment in research and development (R&D). This research, which is performed predominantly by universities and nonprofit institutions, is viewed as a means of providing new ideas for products or processes or of helping firms solve technical problems related to existing

I would like to thank the participants of the conference Evaluation of Government-Funded R&D Activities (Vienna, May 2003) as well as those attending the Econometric Society North American summer meeting at Northwestern University's Kellogg School of Management (June 2003). Comments by Dan Rich, Dennis Carlton, and the anonymous referees were particularly helpful. I would also like to thank Pfizer, Inc., for providing financial support for the data-construction process required for this research. All opinions, analyses, and potential errors are my responsibility.

[*Journal of Law and Economics*, vol. 50 (February 2007)]
 0022-2186/2007/5001-0003$10.00

projects. On the other hand, those who want to discontinue or reduce funding believe that public research substitutes for private investment in R&D. They believe that this research crowds out private investment by drawing important research inputs out of the private sector or simply substitutes for private investment in R&D by funding projects that otherwise would be pursued by industry firms (David and Hall 2000; David, Hall, and Toole 2000).

Recognizing that complementarity and substitutability may happen concurrently and along dimensions that are not completely observable or measurable, existing research focuses on estimation of the net effect of publicly funded R&D on private R&D investment. From a recent survey of the econometric evidence accumulated over the past 35 years, David, Hall, and Toole (2000) reported that most studies find complementarity; however, the overall literature is mixed and inconclusive.[1] The authors note that the net effect found in many studies depends critically on the nature of the public research under investigation, as well as on the particular technological opportunities and appropriability conditions facing private firms.

To limit the influence of unobserved heterogeneity, this paper examines pharmaceutical industry investment within classes of medical technology. Focusing on the pharmaceutical industry eliminates variation from interindustry differences in technological opportunities and appropriability conditions, while distinguishing among classes of medical technology addresses heterogeneity in opportunities across scientific areas of research. As in previous studies (Wiggins 1983; Jaffe 1989; Ward and Dranove 1995), these distinctions enable analysis of the relationship between public and private R&D investment within technology classes over time.

The data and econometric improvements used in this paper are distinct from those used in previous research by Ward and Dranove (1995). Unique and comprehensive grant and contract award data covering all National Institutes of Health (NIH) funding enabled accurate measurement of public research investment in medical classes. For each medical class, the data for public funding of biomedical research was separated by character of research into basic laboratory research and clinical human research. This is a significant advantage because pharmaceutical industry investment responds differently depending on the character of the public research in question. The econometric analysis addressed the endogeneity of industry sales in the R&D investment decision by

[1] Most of this literature is focused on the impact of publicly funded research performed directly by the private firms receiving the money. The current paper considers the impact of public financing of research performed mostly by research scientists at nonprofit institutions and asks how this research affects private investment in research and development (R&D). Guellec and van Pottelsberghe (2003) found that government-funded research performed directly by private firms stimulates additional private investment in R&D, whereas government-funded research performed by universities reduces industry investment in R&D. Although this finding does not support the complementarity hypothesis for publicly financed university research, the authors note that they were only able to allow a 4-year lag in the relationship between university and industry research.

using exogenous measures of hospital admission and mortality rates as instrumental variables (IVs).

Using a panel of seven medical classes over the period 1981–97 and a two-stage least squares (2SLS) methodology, the regression results showed that public basic and clinical research complement private pharmaceutical R&D investment. However, pharmaceutical R&D investment responds differently to each type of public research. For public basic research, which is characterized by a high degree of uncertainty in its scientific maturity and its potential market applicability, changes in pharmaceutical R&D investment have a U shape. Firms respond quickly to new information from public basic research; then, after a period of holding the level of investment constant and allowing scientific and market uncertainties to resolve, firms again increase private R&D investment. This finding is consistent with established theory on investment under uncertainty (Pindyck 1991; Dixit 1992; Dixit and Pindyck 1994). The long-term-elasticity estimate is 1.69 and suggests that a $1.00 increase in public basic research stimulates an additional $8.38 of industry R&D investment after 8 years.

Compared to basic research, public clinical research has very little scientific or market uncertainty, and this difference is reflected in the timing of the investment response by the pharmaceutical industry. The industry R&D response to public clinical research is shorter in duration and smaller in magnitude. The results suggest that firms increase private R&D investment in response to public clinical research within the first 3 years; thereafter, no significant impact was found. The long-term-elasticity estimate is .40 and suggests that a $1.00 increase in public clinical research stimulates an additional $2.35 of industry R&D investment after 3 years.

The paper begins with a discussion of the interaction between public and private research, drawn mainly from case study evidence on pharmaceutical innovation. Section 3 outlines an empirical model of pharmaceutical R&D investment, and Section 4 discusses the data. Section 5 presents the estimation results, and Section 6 contains concluding remarks.

2. Interaction between Public Research and Pharmaceutical Research and Development

How public scientific research influences private R&D investment depends on the nature of the research problems that industry scientists face in the process of pharmaceutical innovation. There are two stages in this process—namely, drug discovery and drug development—and each stage involves a unique set of research activities. Drug discovery, or preclinical research, involves a wide spectrum of laboratory and nonhuman research activities ranging from identification of new drug concepts to the use of animal models and compound patenting. Having identified a promising new compound, drug development follows this stage with a full set of human clinical trials, to determine compound safety and

efficacy, before seeking product approval from the U.S. Food and Drug Administration (FDA).[2]

Paralleling this division of industry research, public research investment also can be separated by the character of research activity.[3] Basic or fundamental biomedical research can be broadly defined as bench-level laboratory research directed at the discovery and characterization of physiologically active substances and the definition of metabolic pathways related to normal and disease function. Public clinical biomedical research is patient-oriented research involving human subjects; it includes epidemiological research but excludes social, behavioral, occupational, and health services research.[4]

In both stages of pharmaceutical research, the overall influence of public research will be determined by the degree to which industry scientists draw from and add to public scientific knowledge. Since it is not feasible to observe, measure, and aggregate data across individual scientists in order to calculate a net flow of knowledge from public research to industry R&D, the interpretation of direction and magnitude established by statistical methods must rely on insights gained from case studies.[5]

There is a substantial body of case study research that describes a predominantly complementary relationship between private-industry R&D investment and public basic research (see Maxwell and Eckhardt 1990; U.S. Congress 1993; Cockburn and Henderson 1997; NIH 2000; Colyvas et al. 2002; Reichert and Milne 2002). Most of this research highlights the role that basic research plays in opening new avenues to therapeutic outcomes. It is useful to think of the new therapies pursued by industry scientists as therapeutic jigsaw puzzles that must be completed before any new drug treatment can be brought to market. Public basic research provides either completely new puzzles or resurrects puzzles that were believed to be unsolvable. In either situation, almost all the case studies characterize the new puzzles emerging from public basic research as embryonic (Colyvas et al. 2002). These puzzles are often in their earliest stages of scientific development and may embody only the faintest outline of a promising new therapy. A key finding from these studies is that public basic research is characterized by a high degree of uncertainty in both its scientific maturity and its potential market applicability.

Beyond supplying new ideas for therapies, public basic research can contribute

[2] The separation of research into medical technology classes is a similar delineation of research problems and solutions by broad character.

[3] Public research is scientific research that is financially supported with public funds and performed almost exclusively in hospitals, not-for-profit research institutes, and universities.

[4] This definition is more restrictive than the definition of clinical research put forth by the Director's Panel on Clinical Research of the National Institutes of Health (NIH 1997). However, the NIH definition of clinical research has been criticized for being too broad (Reichert and Milne 2002).

[5] Public scientific knowledge may influence industry scientists and their work without eliciting a measurable investment response. In the subsequent analysis, the ideas and findings from public scientific research had to be significant enough to influence the rate and direction of private investment in pharmaceutical R&D.

to industry solutions by providing pieces of the puzzle or by providing the clues required for discovering new pieces. In the case studies, these pieces and clues take the form of methods for identification of target compounds, validation of these targets, methods for producing sufficient quantities of the compound for animal and human testing, and the design of laboratory models for animal studies (Arora and Gambardella 1994; Gambardella 1995; U.S. Congress 1993; Cockburn and Henderson 1997; NIH 2000). Because of the complexity and diversity of the puzzles confronting industry scientists, the pieces drawn from public basic research are rarely the "plug and play" variety. Information from this research must be shaped to fit the specific puzzle under investigation. Moreover, when public basic research only provides clues, new pieces must be invented to fit the puzzle.[6]

Although most observers believe that public clinical research is complementary to industry research, there is relatively little case study evidence that sheds light on this interaction.[7] The most specific type of clinical research, the drug trial, is a pure substitute for private-industry research. At least with respect to a specific compound, a publicly supported clinical trial allows the industry to use its R&D resources elsewhere. For instance, if a particular compound is shown to be toxic or ineffective, industry researchers do not need to spend additional funds to duplicate that research. However, the knowledge gained about a compound's absorption, toxicity, elimination, side effects, and efficacy may provide valuable information to industry scientists. Using the specific knowledge gained from a publicly supported clinical trial, industry researchers might investigate a modified compound from the same chemical family or a modified dosage regime and find a safe and effective drug.

Cockburn and Henderson (1997) have suggested that publicly supported clinical research plays an important role in the process of finding new uses for older drugs. If promising new indications are revealed from early-phase clinical trials performed in the public sector, the industry may choose to pursue the full complement of clinical trials necessary for FDA approval. This type of follow-on complementarity also may arise when market uncertainty is too high to elicit private investment. Gelijns, Rosenberg, and Moskowitz (1998) suggested that public-sector clinical researchers may have an important role to play in reducing uncertainty and perhaps facilitating the adoption of new drug candidates by industry firms. Moreover, public epidemiological studies help the industry gauge

[6] The discussion here encompasses the idea of absorptive capacity, which posits that private firms must be actively investing in research in order to access, evaluate, and use public scientific knowledge (Cohen and Levinthal 1989; Arora and Gambardella 1994).

[7] Maxwell and Eckhardt (1990, p. xxiii) found that clinical research played an important role in the initiation of 23 percent of the 30 lines of research in their study. However, they define the term "clinical" to mean that "the research was carried out in humans or human material." In this paper, clinical research is defined to include only research involving patients. Consequently, research using human material is included in the basic research category. Flowers and Melman (1997) focus on the role of academic clinical investigators in the development of five purine analogue drugs discovered at private pharmaceutical firms.

demand for new therapies in patient populations. These alternative types of public clinical research are likely to stimulate additional investment by the industry.[8]

The most recent empirical study of the relationship between public and private R&D investment in the pharmaceutical industry was conducted by Ward and Dranove (1995). Their analysis related pharmaceutical R&D investment to NIH research obligations, using a panel of five medical therapeutic classes, between 1970 and 1988. The authors' data did not enable them to differentiate between basic and clinical research. Instead, they used total financial obligations by NIH institute (such as the National Cancer Institute, the National Heart, Lung, and Blood Institute, and others) as a measure of public basic research in each therapeutic class. Unfortunately, NIH obligations by institute are a diverse set of financial commitments that includes basic and clinical research and administrative, training, demonstration, construction, and other activities. The authors' main finding indicated that a 1 percent increase in NIH research obligations leads to an increase in industry R&D of .6–.7 percent after a lag of 7 years.

3. A Model of Pharmaceutical Research and Development Investment

The empirical model of pharmaceutical R&D investment presented below follows the investment framework described by David, Hall, and Toole (2000). This framework is commonly used in the literature and has been applied to pharmaceutical R&D investment through the use of firm-level data, by Grabowski and Vernon (1980, 2000), and industry-level data, by Giaccotto, Santerre, and Vernon (2005). The model postulates that the level of investment is determined by the interaction between the marginal cost of capital (MCC) and the marginal rate of return (MRR). Factors that affect the availability of funds, such as sales revenue and interest rates, determine the shape and position of the MCC schedule. Factors that affect the demand, cost, and probability of success in research, such as health status, FDA regulatory stringency, and public scientific knowledge, determine the shape and position of the MRR schedule. Together, these schedules are used to determine the equilibrium level of investment.

In the empirical model used in this study, this framework is specified across classes of medical technology. The factors affecting the availability of funds include gross revenues from sales and dummy variables that account for differences across classes and shifts over time owing to, among other factors, changes in the cost of capital. Factors that affect the return on industry investment include measures of demand, proxies for public basic and clinical scientific knowledge, FDA regulation, and dummy variables that account for differences across classes

[8] Empirical studies in the literature have attempted to measure the connectedness between public and private research and to relate the degree of connectedness to productivity in the pharmaceutical industry. Cockburn and Henderson (2001) provide a good overview of the literature, but this literature is not central to the current analysis. This analysis explores the relationship between R&D inputs but not how public research directly impacts industry productivity.

and shifts over time owing to, among other factors, changes in drug regulations. The reduced-form fixed-effects model for an individual therapeutic class i in year t is as follows:

$$I_{it} = \beta_0 + \beta_1 S_{i(t-1)} + \sum_{j=1}^{9} \alpha_j B_{i(t-j)} + \sum_{j=1}^{9} \varphi_j C_{i(t-j)} + \beta_2 R_{i(t-1)} + \boldsymbol{X}'\delta + \theta_i + \lambda_t + \varepsilon_{it}, \quad (1)$$

where I_{it} is the natural log of industry R&D investment and $S_{i(t-1)}$ is the natural log of sales revenue in class i in the previous year, $t - 1$. Gross sales revenue is a measure of the availability of funds for R&D investment and is lagged by 1 year to reflect the pharmaceutical budgeting process (Grabowski and Vernon 2000).[9] The terms $B_{i(t-j)}$ and $C_{i(t-j)}$ are distributed lags of the log of public basic and clinical research investment in class i and year $t - j$. The data allow these distributed lags to extend back 9 years prior to industry investment. The term $R_{i(t-1)}$ is the natural log of the FDA regulatory delay in the previous year, and $\boldsymbol{X}$ is a vector of the log of measures of drug demand for class i and year t. A subgroup of these measures, which have no effect on industry R&D, is potential instruments for industry sales. The unobserved effect of therapeutic class i is θ_i, and the yearly time dummies are λ_t. An idiosyncratic error with the standard properties is indicated by ε_{it}.

To estimate equation (1), the industry R&D series must be weakly dependent. However, when a standard Dickey-Fuller test was used, rejection of the null hypothesis that industry R&D is a unit root process was not possible.[10] High persistence in the pharmaceutical investment series is hardly surprising, since development of a new drug takes an average of 12–15 years.[11] To make the series weakly dependent, the analysis used the log-difference estimator, which eliminated the fixed effects of therapeutic class and specified the equation in terms of growth rates. The new estimation equation is as follows:

$$\Delta I_{it} = \beta_1 \Delta S_{i(t-1)} + \sum_{j=1}^{8} \alpha_j \Delta B_{i(t-j)} + \sum_{j=1}^{8} \varphi_j \Delta C_{i(t-j)} + \beta_2 \Delta R_{i(t-1)} + \Delta \boldsymbol{X}'\delta + \Delta\lambda_t + \Delta\varepsilon_{it}. \quad (2)$$

[9] Scherer (2001) examined the relationship between gross profitability and pharmaceutical R&D. Vernon (2005) noted that industry sales serve as proxy for two influences: expected profitability and internal funds for investment. Since the model used here already includes controls for demand that influence expected profitability, the partial effect of gross sales was interpreted as a measure of the impact of internal financing. The availability of internal funds for financing investment is important when capital markets are imperfect. See Hall (forthcoming) and Hubbard (1998) for an overview.

[10] A Dickey-Fuller test with trend and an augmented Dickey-Fuller test were also performed. The null hypothesis of a unit root for industry R&D was not rejected by either test. In addition, the augmented Dickey-Fuller test did not indicate any dynamic misspecification.

[11] In their analysis using proprietary firm data, Henderson and Cockburn (1996) also found high persistence in the pharmaceutical R&D process.

The main hypotheses are that public basic and clinical research complement industry R&D investment in the long term. To reduce multicollinearity and smooth the private-investment response, the finite distributed lags for public basic and clinical research were restricted to lie on a second-degree polynomial. These are commonly referred to as Almon lags.[12] Over time, the estimated lag coefficients for public research may be investment stimulating (positive lag coefficient) or investment saving (negative lag coefficient) for the industry, depending on the nature and evolution of research projects in each sector. The long-term elasticity was calculated as the sum of the statistically significant lag coefficients. A positive long-term elasticity was interpreted as evidence supporting complementarity in which public research stimulates additional private pharmaceutical R&D investment. A negative long-term elasticity, however, would not be conclusive evidence for substitution. Substitution has the additional requirement that firms would have undertaken the research themselves, which could not be determined from the available data.

In equation (2), growth in sales, $\Delta S_{i(t-1)}$, should be viewed as endogenous. A common rule of thumb for industry executives is to set R&D investment as a fixed proportion of sales (Grabowski and Vernon 1980, 2000). Moreover, in a review of research in this area, Scherer (1996, p. 269) noted that industry R&D growth may simply reflect an endogenous response to "the actual rise in gross profitability," instead of changes in response to "richer technological opportunities." Scherer (2001) explored this relationship further by using industry time-series data and found a positive relationship between gross profitability and R&D spending. Moreover, causation was found to be reciprocal, with R&D spending ultimately feeding back to determine sales revenue. This feedback is a violation of the assumption of strict exogeneity needed for the consistency of estimators.

To correct for endogeneity, I needed instruments that did not belong in industry R&D investment equation (2) but that were highly correlated with industry sales. Valid instruments could come from the group of hospital admission and mortality rate demand measures, as long as they met the above-mentioned two conditions. In the empirical analysis, I used a two-step approach: First, I determined the potential set of instruments from the demand variables by determining which of these variables were appropriately excluded from the investment model. Next, from the set of potential instruments, I determined which of these instruments had a strong partial correlation with pharmaceutical sales. Any demand measures that met these criteria were considered to be valid instruments. Note that the instruments were determined exogenously in the patient population and were not under the direct control of the pharmaceutical R&D

[12] I would like to thank the editor for suggesting this formulation. An earlier draft of this research left the lag coefficients completely unrestricted. Imposing the polynomial restrictions led to slightly larger coefficient estimates but did not change the research findings. These restrictions did facilitate interpretation, however, by elimination of fluctuations in the lag estimates that resulted from multicollinearity between the public research flows. Hall, Griliches, and Hausman (1986) also analyzed polynomial lags.

decision makers. For the empirical model, I assumed that these measures were strictly exogenous.

Although the empirical model described in this paper improves on those found in the current literature, two modeling limitations should be noted and addressed in future research. First, better data would allow estimation of a structural model that explicitly characterizes the channels through which public research and private R&D interact. At this point, research efforts intended to explore channels such as publications and personal networks face significant data limitations. The model described in this paper treated the channels as an implicit "black box."[13]

Second, the model assumes that public research investment is exogenous to private R&D decisions made by pharmaceutical firms. This assumption is reasonable, since pharmaceutical R&D decision makers have no direct control over the quantity or allocation of federal research funding. On the basis of the lags in the model, public research is clearly a predetermined variable; however, this assumption rules out feedback from current industry R&D to future public research investment. Failure of the assumption of strict exogeneity can lead to inconsistency in the estimators. These limitations should be kept in mind when interpreting the empirical results.

4. Data and Descriptive Statistics

To estimate the impact of public basic and clinical research on industry investment, I analyzed observations from 1981 to 1997 for a panel of seven medical therapeutic classes. The medical therapeutic classes are defined by the U.S. Department of Commerce Census Bureau. This classification scheme has been used by the pharmaceutical industry to group R&D and sales data since the early 1960s. The following seven therapeutic classes were considered: endocrine/neoplasm (cancer), central nervous system, cardiovascular, anti-infective, gastrointestinal/genitourinary, dermatologic, and respiratory. Table 1 presents summary statistics by therapeutic class for many of the variables used in this analysis.

The empirical analysis used public investment in basic and clinical research as proxies for the generation of scientific knowledge. The proxies are defined by use of detailed data on grant and contract awards by the U.S. Department of Health and Human Services (DHHS), particularly the NIH. The NIH is the largest public agency in the world that supports biomedical research. Its budget was doubled in the 5-year period between 1998 and 2003 and is $28.6 billion for fiscal year 2006. Furthermore, the American Association for the Advancement of Science (2006) reports that the NIH is the second largest public agency supporting R&D in the United States, after the Department of Defense, and the largest agency supporting undirected, or basic, research.

The limitations of using investment flows as proxies for knowledge generation

[13] See Cohen, Nelson, and Walsh (2002) to learn about the many channels that link public and private R&D. Also see Cockburn and Henderson (2001) for a review of recent empirical work using measures that focus on specific channels such as publication coauthorships.

Table 1

Summary Statistics, by Medical Therapeutic Class

Variable	Endocrine/Neoplasm (Cancer)	Central Nervous System	Cardiovascular	Anti-infective	GI/GU	Dermatologic	Respiratory
Industry R&D investment:							
Mean ($)	2,645.36	2,290.40	2,692.80	2,918.47	729.75	837.79	268.97
SD ($)	1,457.95	771.51	1,179.88	534.89	128.57	298.77	87.11
Average growth, 1981–97 (%)	9.7	6.4	8.0	4.6	4.0	7.1	0.9
Industry sales:							
Mean ($)	20,891.10	18,268.00	14,594.50	19,555.00	11,578.90	6,408.20	2,726.90
SD ($)	2,976.90	1,797.40	5,467.00	4,682.50	3,801.10	1,621.40	636.10
Average growth, 1981–97 (%)	2.1	1.4	4.5	4.4	5.4	4.0	3.4
NIH public research investment:							
Basic:							
Mean ($)	1,393.99	818.52	593.71	644.62	355.97	23.97	154.65
SD ($)	109.63	149.96	58.10	171.83	21.29	4.47	26.07
Average growth, 1981–96 (%)	1.5	3.5	1.4	4.9	−.2	1.6	3.1
Clinical:							
Mean ($)	1,123.26	769.87	337.20	277.71	109.57	4.90	65.47
SD ($)	199.47	358.15	65.34	186.55	20.92	3.13	13.52
Average growth, 1981–96 (%)	2.0	7.6	3.1	15.0	1.4	14.6	3.1
Hospital admission rate (all ages):							
Mean (per 1,000 population)	102.14	122.43	199.20	54.04	122.35	7.54	54.64
SD (per 1,000 population)	18.89	31.61	10.22	5.62	23.05	3.44	6.34
Average growth, 1981–97 (%)	−3.4	−3.7	−.4	1.9	−3.4	−8.0	−1.2
Mortality rate (all ages):							
Mean (per 1,000 population)	19.29	2.25	33.00	3.68	3.68	.09	3.68
SD (per 1,000 population)	.50	.57	3.07	.66	.11	.01	.41
Average growth, 1981–97 (%)	.4	5.1	−1.7	2.7	−.3	−1.8	2.4
FDA regulatory delay:							
Mean (months)	31.41	36.90	38.27	24.11	25.91	22.49	51.13
SD (months)	22.60	12.53	9.78	8.50	12.68	7.57	23.78
Average growth, 1981–96 (%)	−5.9	−4.5	1.7	.4	−1.5	−.1	−7.0

Note. All dollar figures are in millions with base year 2000. Data sources and variable definitions are described in the text. GI/GU = gastrointestinal/genitourinary; R&D = research and development; NIH = National Institutes of Health; FDA = U.S. Food and Drug Administration.

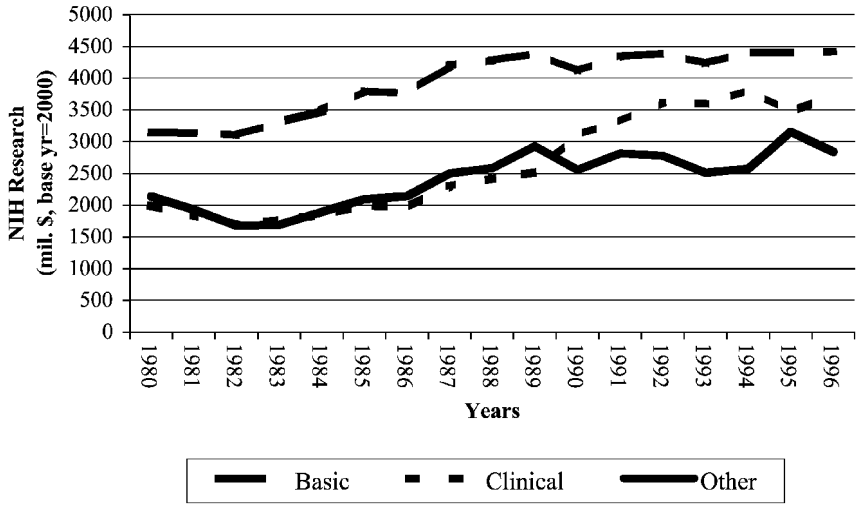

Figure 1. Biomedical research investment by the National Institutes of Health (NIH), by research type.

are well known, but investment flows have at least three advantages over other measures of knowledge creation. First, other indicators, such as patents and publication counts (perhaps weighted by frequency of citation), capture only one form of codified knowledge. In principle, investment proxies are general enough to capture all forms of knowledge creation, either codified or tacit. Second, investment flows are not restricted to any particular channel of dissemination. The use of published journal articles, on the other hand, misses public research flows that happen through conferences, networks, or consulting. Third, other indicators of research output are not under the control of policymakers, whereas the allocation of public funds for research is one of the most important policy tools available.

The investment proxies for public basic and clinical research knowledge were defined by use of the Computer Retrieval of Information on Scientific Projects (CRISP) database, which is maintained by the NIH. These data contain specific information about each biomedical grant and contract awarded by the NIH and other agencies in the DHHS. A multistage procedure was used to separate these data by character of research (basic, clinical, or other) and to further allocate grants and contracts to therapeutic classes (the Appendix gives a detailed description of this procedure). The data procedure resulted in seven public basic research flows and seven public clinical research flows for each year over the period 1972–96. These flows were deflated by use of the NIH Biomedical Research and Development Price Index, maintained by the Bureau of Labor Statistics (BLS), with a base year of 2000. Figure 1 shows the broad-level distribution of

NIH research investment in basic, clinical, and other research types, in real dollars.[14]

Data on pharmaceutical industry investment and sales by therapeutic class were gathered from the Pharmaceutical Research and Manufacturers of America (PhRMA; 1980–99). The R&D data correspond to R&D investment by PhRMA members in the United States and abroad. The sales figures correspond to total industry sales, including sales by non-PhRMA members, in the United States and sales by U.S. companies abroad. The nominal flows were deflated by use of the BLS Producer Price Index for Pharmaceutical Preparations, with a base year of 2000.

Regulatory stringency proxies by therapeutic class and year were constructed by use of data from the FDA. As in Wiggins (1983), the proxy was defined to be the average delay, in months, between the date of submission of a new drug application and the date of FDA marketing approval. If more than one compound was approved in a particular therapeutic class, then the regulatory delay variable was an arithmetic average of the observed review periods. For instance, if a therapeutic class had two approved drugs in a particular year, one with a 10-month delay and the other with a 14-month delay, then the delay period used in the analysis was 12 months. This averaging methodology is intended to capture how pharmaceutical firms adjust their expectations of FDA regulatory review.

The demand variables and potential instruments used were hospital admission and mortality rates, by therapeutic class and year, for five age groups. These data were gathered from the National Center for Health Statistics and were grouped by therapeutic class in accordance with U.S. Department of Health and Human Services (2004). The three-digit diagnosis level was used for classification, for each of the following five age groups: <35 years, 35–44 years, 45–54 years, 55–64 years, and $\geqslant 65$ years. For each therapeutic class and age group, the hospital admission rates came from the National Hospital Discharge survey and were defined per 1,000 population. The mortality rates came from the multiple-cause-of-death file of the National Vital Statistics System and also were defined per 1,000 population.

5. Estimation Results and Discussion

The empirical analysis was done in two steps. The first step consisted of three pooled ordinary least squares (OLS) regressions that were used to determine which variables belonged in the model. This first step was necessary because it was unknown which of the hospital admission and mortality rate demand variables were potential instruments for pharmaceutical sales. If these variables have a significant effect on pharmaceutical R&D, then they should not be excluded from the model and are not valid IV candidates. Having determined the IV

[14] Because of space limitations, figures for each of the seven medical therapeutic classes have been omitted. These figures are available from the author upon request.

Table 2

Ordinary Least Squares Regression Results: $\Delta\ln(\text{Industry R\&D})_t$

Dependent Variable	(1)	(2)	(3)
Δln(Public basic research):			
Polynomial term 1	.341** (.134)	.343** (.115)	.347** (.112)
Polynomial term 2	−.320** (.081)	−.276** (.073)	−.271** (.075)
Polynomial term 3	.045** (.011)	.039** (.010)	.038** (.010)
Δln(Public clinical research):			
Polynomial term 1	.109* (.049)	.077+ (.047)	.093* (.046)
Polynomial term 2	−.042 (.029)	−.031 (.026)	−.036 (.026)
Polynomial term 3	.005 (.004)	.003 (.003)	.003 (.003)
$\Delta\ln(\text{Industry sales})_{(t-1)}$	.198 (.158)	.059* (.030)	.073** (.030)
$\Delta\ln(\text{FDA delay})_{(t-1)}$	.018 (.017)	.008 (.017)	
Δln(Hospital admission rate), by age group:			
<35 Years	−.254 (.193)	−.280 (.179)	
35–44 Years	−.032 (.149)	−.071 (.141)	
45–54 Years	.081 (.129)	.138 (.125)	
55–64 Years	.558** (.176)	.586** (.173)	.571** (.153)
⩾65 Years	−.589** (.207)	−.319+ (.186)	−.410* (.182)
Δln(Mortality rate), by age group:			
<35 Years	.132 (.102)	.124 (.103)	
35–44 Years	−.212+ (.114)	−.220* (.111)	−.216** (.080)
45–54 Years	−.061 (.148)	−.032 (.132)	
55–64 Years	.632* (.296)	.669* (.283)	.692** (.237)
⩾65 Years	−.107 (.299)	−.285 (.276)	
Time trend		.063** (.021)	.060** (.019)
Diagnostic:			
R^2	.407	.313	.262
Adjusted R^2	.166	.190	.190
Durbin-Watson statistic	1.96	1.87	1.94

Note. Data are pooled results for the years 1981–97, for seven medical therapeutic classes, and are based on 119 observations. Standard errors are in parentheses. All tests were two sided. Yearly time dummies were not significant in model 1 and were replaced by a time trend in models 2 and 3. R&D = research and development; FDA = U.S. Food and Drug Administration.

+ $p < .10$.

* $p < .05$.

** $p < .01$.

candidates and verified their partial correlation with pharmaceutical sales, the second step in the analysis consisted of three pooled 2SLS regressions.

Before discussion of the actual estimates, it is important to recall that the lag distributions for public basic and clinical research were specified as second-degree polynomials.[15] The coefficient estimates for the quadratic polynomial terms are reported in Tables 2 and 3. The implied lag-coefficient estimates and their statistical significance will be discussed with the final specification of the 2SLS model. Regression diagnostics are given at the bottom of Tables 2 and 3.

The results of the OLS regression analysis are given in Table 2. Column 1 corresponds to the fully specified model, which included all the available ex-

[15] Higher-order polynomial terms were not significant for either public basic research or public clinical research.

Table 3

Two-Stage Least Squares Regression Results: $\Delta\ln(\text{Industry R\&D})_t$

Dependent Variable	(1)	(2)	(3)
Δln(Public basic research):			
Polynomial term 1	.494** (.181)	.582** (.210)	.607** (.218)
Polynomial term 2	−.327** (.105)	−.339** (.131)	−.372*** (.134)
Polynomial term 3	.045** (.014)	.047** (.017)	.052** (.018)
Δln(Public clinical research):			
Polynomial term 1	.163* (.079)	.211* (.088)	.172* (.072)
Polynomial term 2	−.064 (.040)	−.075 (.047)	−.038* (.018)
Polynomial term 3	.005 (.004)	.005 (.005)	
$\Delta\ln(\text{Industry sales})_{(t-1)}$	.344+ (.203)	.481* (.215)	.498* (.223)
Δln(Hospital admission rate), by age group:			
55–64 Years	.637** (.204)	.579* (.253)	.546* (.251)
⩾65 Years	−.202 (.281)		
Δln(Mortality rate), by age group:			
35–44 Years	−.333* (.135)	−.391* (.157)	−.380* (.158)
55–64 Years	.856** (.330)	.867* (.412)	.872* (.424)
Time trend	.042 (.027)		
Diagnostic:			
R^2	.171	.173	.165
Adjusted R^2	.086	.097	.097
Durbin-Watson statistic	1.93	1.90	1.96

Note. Data are pooled results for the years 1981–97, for seven medical therapeutic classes, and are based on 119 observations. Standard errors are in parentheses. All tests were two sided. R&D = research and development.

+ $p < .10$.

* $p < .05$.

** $p < .01$.

planatory variables, including yearly time dummies. Since the yearly time dummies were not jointly or individually significant, the model in column 2 replaced these variables with a time trend. Model 3 adjusted the specification by dropping the other insignificant regression variables.

Comparison of the regression results in Table 2 reveals that both public basic and public clinical research significantly impact the growth of pharmaceutical R&D investment. The quadratic specification worked well for public basic research; however, both the linear and quadratic terms were insignificant for public clinical research. This result will be addressed in the 2SLS regression analysis in Table 3. Growth in pharmaceutical sales was significant in models 2 and 3, in which the yearly time dummies were dropped and replaced with a linear time trend. The insignificance of industry sales in model 1 was probably due to multicollinearity between industry sales and the yearly time dummies. The effect of FDA regulatory delay, which was a proxy for regulatory stringency, was not economically or statistically significant in either model 1 or 2 and was dropped in model 3.

With regard to the patient demand variables, four of the 10 variables were significant. The results indicate that pharmaceutical R&D investment increases strongly in response to the health conditions of people in the age group 55–64

years. These conditions drive increases in hospital admission and mortality rates. However, growth in pharmaceutical R&D investment falls in response to an increase in the hospital admission rate for people 65 and older. Why this occurs is difficult to know but could reflect the fact that the hospital admission rate for the oldest age group are for conditions that are not amenable to drug therapy. In addition, growth in pharmaceutical R&D investment was found to decrease with an increase in mortality rate among those in the age group 35–44 years. This finding probably reflects an expected fall in the return on investment as these potential customers are lost.

Although an OLS regression analysis is a proper place to start, Scherer (2001) noted that the volume of pharmaceutical sales is an endogenous variable in a model of pharmaceutical R&D investment. On one hand, an increase in sales leads to more R&D investment, either by providing internal funds for investment or by capturing expected demand; on the other hand, current R&D investment leads to future sales. Of the six potential IV candidates identified in the first step of this analysis, the hospital admission rate for people less than 35 years old was the only valid IV. This variable had a strong partial correlation with pharmaceutical sales in a first-stage regression, with a t-statistic of -2.19 and a p-value of $<.03$, whereas the other variables had no significant partial correlation with pharmaceutical sales. Consequently, one valid IV was available, and the 2SLS regression results presented in Table 3 are just identified.

The model in column 1 of Table 3 used the same specification as model 3 in Table 2. As is typical in an IV regression, the standard errors were larger than those in the OLS regressions; consequently, the hospital admission rate variable for people 65 and older was insignificant. The time trend also was insignificant. The model in column 2 dropped these variables. The final model, given in column 3, tightened the specification for public clinical research. High multicollinearity between the polynomial terms for public clinical research was the likely culprit for the insignificance of the linear and quadratic terms; however, these terms were not jointly significant when a standard F-test was used. Dropping the quadratic term dramatically reduced the standard errors for public clinical research; thus, the linear term was now significant. This confirmed the presence of multicollinearity. Although model 3 is used in the subsequent discussion, model 2 could easily be used as well. The only difference between the models is that model 3 gave slightly larger magnitudes for the effects of public basic and clinical research, whereas model 2 provided a more intuitive shape (quadratic versus linear) for the lag distribution for public clinical research.

The empirical analysis found strong evidence that public basic research is complementary to private pharmaceutical R&D investment and thereby stimulates additional private investment. Figure 2 shows a graph of the underlying lag coefficients for public basic research based on the estimated polynomial parameters in model 3 of Table 3; the coefficient estimates are given in Table 4. Each of these lag coefficients is an elasticity that measures the percentage change in the growth of pharmaceutical R&D investment in response to a 1 percent

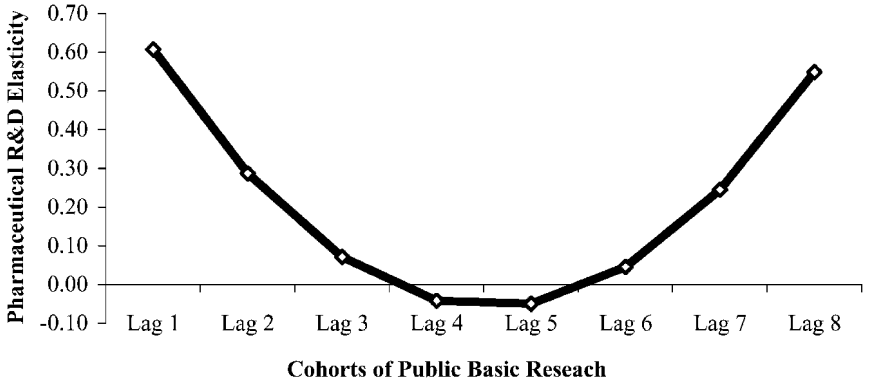

Figure 2. Elasticity estimates of pharmaceutical research and development (R&D) investment in response to cohorts of public basic research.

increase in the growth of public investment in basic research. Only four of the eight lag coefficients for public basic research reported in Table 4 are significantly different from zero. These are the first two and the final two lag coefficients. By use of a two-sided test, the *p*-values for lag coefficients 1, 2, 7, and 8 were found to be <.006, <.034, <.026, and <.002, respectively. Long-term elasticity, which is the sum of the statistically significant lag coefficients across time, was 1.69, which is more than twice the elasticity found by Ward and Dranove (1995); however, the estimates are not directly comparable, since Ward and Dranove's analysis used a very different model and data.

As shown in Figure 2, the industry response over time to public investment in basic research has a U shape. Public investment is a proxy for scientific knowledge generated by research institutions outside the pharmaceutical industry, primarily universities. Scientific knowledge generated by basic research is characterized by a high degree of uncertainty with respect to both its scientific maturity and its potential market application. The newest ideas emerging from public basic research are the most uncertain and will be reflected in the first lag. With each successive year, these ideas are developed further by researchers in public research institutions. As the idea "ages" and moves through the lag distribution, many of the scientific and market uncertainties will be resolved. The latter part of the lag distribution—that is, lags 7 and 8—represent knowledge from public basic research that has evolved through 7 or 8 years of further refinement.

To understand the time profile of the private pharmaceutical investment response, the theory of investment under uncertainty is helpful (Pindyck 1991; Dixit 1992; Dixit and Pindyck 1994). A fundamental insight of this work is that a firm's optimal investment response can involve waiting or delaying investment until uncertainties have been resolved sufficiently. Furthermore, the theory notes

Table 4

Elasticity of Pharmaceutical Research and Development Investment

Cohorts of Public Research	Public Basic Research	Public Clinical Research
Lag 1	.607** (.218)	.172* (.072)
Lag 2	.287* (.133)	.134* (.057)
Lag 3	.071 (.109)	.095* (.044)
Lag 4	−.041 (.117)	.057 (.036)
Lag 5	−.050 (.117)	.019 (.036)
Lag 6	.046 (.106)	−.019 (.044)
Lag 7	.245* (.109)	−.058 (.057)
Lag 8	.548** (.173)	−.096 (.072)

Note. Data are the distributed lag elasticity estimates implied by the polynomial restrictions used in model 3 in Table 3. Standard errors are in parentheses. All tests were two sided.

* $p < .05$.

** $p < .01$.

that the value of waiting depends on the degree of uncertainty and the degree of interfirm competition. More uncertainty increases the value of waiting, whereas competition reduces the value of waiting.[16]

The results shown in Figure 2 illustrate both a competitive effect and a waiting effect. The newest ideas emerging from public basic research elicit an initial burst of investment by pharmaceutical firms as they try to incorporate this new information, build absorptive capacity, and compete with rival firms. This response is a competitive buy-in effect. After this initial burst, firms maintain their research programs and monitor research progress at universities and other research institutions. This is the period in which firms exercise their option to wait and do not significantly increase investment. When scientific and market uncertainties are resolved sufficiently, an average of 7 years after the emergence of the original idea, pharmaceutical firms again significantly increase their investment in response to public basic research.[17] Note that the level of private investment does not fall during this period. Figure 3 shows how the level of private pharmaceutical R&D investment responds over time to a marginal increase in public basic research.

[16] The value of waiting is unambiguously positive when investment is at least partially irreversible and expandable. Investment in R&D is probably one of the most irreversible categories of firm investment. See Abel et al. (1996) for a theoretical treatment and Carruth, Dickerson, and Henley (2000) for a survey of the theoretical and empirical literature.

[17] An anonymous referee suggested the possibility that the industry response to the newest public research ideas, as captured by lags 1 and 2, could be spurious and could simply represent a simultaneous public- and private-investment response to some scientific breakthrough. If this were true, public and private investment would be contemporaneously correlated, as both groups of decision makers respond to the breakthrough. To explore this possibility, contemporaneous public investment was included in the model but was found to always be insignificant, with a coefficient near zero. Although pharmaceutical decision makers clearly are responding to the most promising research findings emerging from publicly funded research, there does not appear to be any omitted source of scientific breakthroughs that induces a simultaneous reaction by both public and private investors.

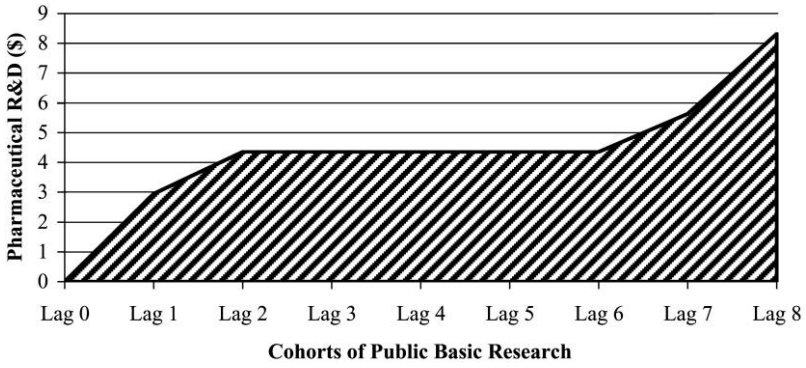

Figure 3. Impact on the level of pharmaceutical research and development (R&D) investment from a marginal increase in public basic research.

The empirical analysis also found strong evidence that public clinical research is complementary to private pharmaceutical R&D investment and thereby stimulates additional private investment. However, relative to public basic research, public clinical research has very little scientific or market uncertainty. Accordingly, the value of waiting is much smaller, and firms would be expected to respond quickly to new and valuable information, particularly when competitive pressures are strong. This is exactly the pattern that emerged from the analysis. Figure 4 shows that pharmaceutical R&D investment increased in the first 3 years after public investment in clinical research. Subsequently, no significant change in private investment was found, as public clinical research aged. Table 4 gives the implied lag-coefficient estimates from model 3 in Table 3. By use of a two-sided test, the *p*-values for the first three lags for public clinical research were found to be <.018, <.02, and <.032. The sum of the coefficient estimates for these three lags gave a long-term elasticity for public clinical research of .40. Figure 5 shows how the level of private pharmaceutical R&D investment responds over time to a marginal increase in public clinical research.

The results from model 3 in Table 3 also indicate that changes in pharmaceutical sales and patient demand influence the growth in pharmaceutical R&D investment. When the impact of expected demand on pharmaceutical R&D investment was held constant, the partial effect of pharmaceutical sales measured how changes in the availability of internal funds affects pharmaceutical R&D investment.[18] A 10 percent increase in internal funds led to a 5 percent increase

[18] As noted by an anonymous referee, the pharmaceutical sales data used in the analysis included sales by firms that are not members of the Pharmaceutical Research and Manufacturers of America (PhRMA), as well as sales by PhRMA members. In theory, the sales data should represent only PhRMA member firms. However, since aggregate totals showed that sales by firms that are not PhRMA members make up a small portion of total market sales, inclusion of these data is unlikely to have significantly influenced the results.

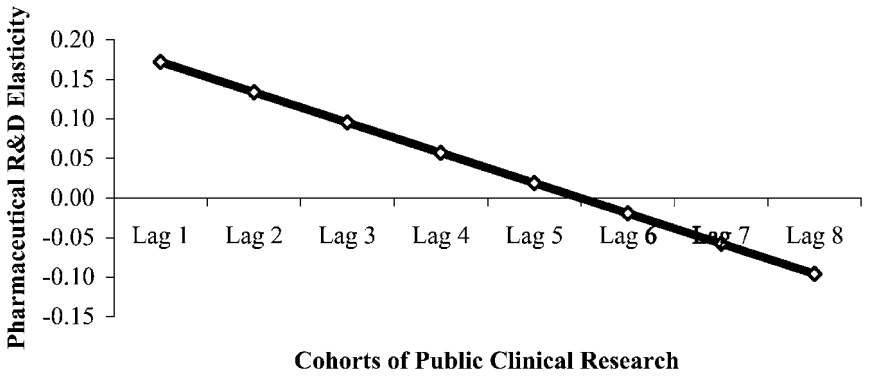

Figure 4. Elasticity estimates of pharmaceutical research and development (R&D) investment in response to cohorts of public clinical research.

in R&D investment; this effect was strongly significant, with a p-value of $<.05$. In a previous study, Giaccotto, Santerre, and Vernon (2005) found a slightly higher elasticity of .58; however, their estimate included both cash flow and expected demand effects. With respect to the demand variables included in model 3, the results were qualitatively similar to those of the OLS specification reported in Table 2.

For policymaking purposes, calculation of the marginal impacts of the key explanatory variables on pharmaceutical R&D investment is informative. Marginal impact was calculated as the product of long-term elasticity and the ratio of the sample average of pharmaceutical R&D investment to the sample average of the variable of interest. Consequently, marginal impacts depended on the relative magnitudes of the measured variables. In Table 5, data are given for public basic research investment, public clinical research investment, and industry sales. A $1.00 increase in public basic research generated an $8.38 increase in private pharmaceutical R&D investment after 8 years. A $1.00 increase in public clinical research generated a $2.35 increase in private R&D investment after 3 years. With respect to industry sales, each new dollar of revenue increased the following year's R&D investment by 8 cents.

6. Conclusions

This paper examines the relationship between publicly financed biomedical research, which is performed mainly by university and nonprofit research laboratories, and the investment behavior of private pharmaceutical firms. The main question in this paper is whether public basic and clinical research complement private R&D investment by the pharmaceutical industry. An increase in industry investment in response to public research, perhaps reflecting the genesis of new projects or the further development of embryonic ideas, is strong evidence sup-

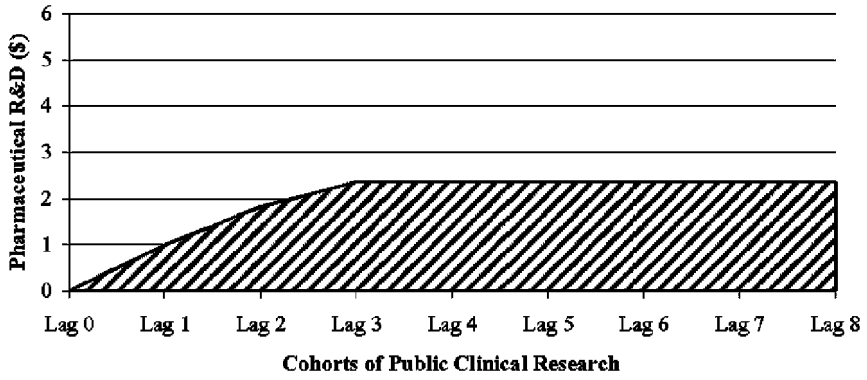

Figure 5. Impact on the level of pharmaceutical research and development (R&D) investment from a marginal increase in public clinical research.

porting a complementary relationship. The analysis found that both public basic research and public clinical research stimulated additional private pharmaceutical R&D.

There are three other notable conclusions stemming from this research. First, to evaluate how private investment responds to public research investment, consideration of the character of the public research under investigation is critically important. The information content and the degree of uncertainty that characterize the public research will impact both the magnitude and timing of the investment behavior of firms. Second, the pharmaceutical investment response to public basic research is more than 3.5 times larger than the response to public clinical research, which suggests that public basic research is more important to the pharmaceutical innovative process than is public clinical research. However, Figure 1 indicates that the NIH has dramatically increased clinical research investment, relative to basic research investment, since the early 1990s. This trend probably will reduce future opportunities for new-drug innovation that stem from public research. Third, this analysis found that internal cash flow is an important determinant of pharmaceutical R&D investment. If price controls on pharmaceutical products are put in place, as many policymakers favor, pharmaceutical R&D investment will decline.

Although this paper improves on both the data and the econometric method used in previous research, the empirical findings should be viewed as suggestive rather than definitive. The diverse and interactive qualities of public and private research in the pharmaceutical industry make it difficult to pinpoint individual effects and attach causal interpretations. Future research should focus on the development of empirical models of public-private interaction that allow the channels of information exchange to be identified and that allow for feedback from private-industry R&D investment to public research investment.

Table 5

Long-Term Marginal Impacts on Pharmaceutical Research and Development (R&D) Investment

Variable	Public Basic Research	Public Clinical Research	Industry Sales
Long-term elasticity	1.69	.40	.50
Ratio (industry R&D/variable)	4.96	5.86	.16
Marginal effect ($)	8.38	2.35	.08

Note. The base year for all real dollars is 2000. Marginal impacts were calculated as the mean of the relevant variables. Elasticity ε is equivalent to $(\partial I/\partial X) \times (X/I)$, where X represents the individual explanatory variable and I represents average industry R&D investment. The marginal effects were calculated as $(\partial I/\partial X) = \varepsilon(I/X)$. The calculation used average industry R&D investment across all therapeutic classes in 1997 ($3,069.954 million), average public clinical research investment for 1996, 1995, and 1994 ($523.976 million), average industry sales in 1996 ($19,227.81 million), and average public basic research in 1996, 1995, 1990, and 1989 ($618.934 million).

Furthermore, the literal interpretation of marginal impacts should be made cautiously. In this analysis, NIH investment flows were used as proxies for all public research investment. Clearly, contributions to investment are made by other public institutions in the United States and abroad. Under the assumption that NIH funding flows provide a good relative picture of public basic versus clinical research investment, the log-log functional form implies that the elasticity estimates are valid, even without inclusion of figures for total worldwide investment in public research. However, this implication is not the same for the calculation of marginal impacts, because these estimates depend on accurate figures for total worldwide investment in public basic and clinical research. For instance, if the NIH represents 50 percent of total worldwide investment in public basic and clinical research (a number that probably underestimates the NIH's share), then the marginal impacts are scaled down by 50 percent.

It is also important to note that the public basic and clinical research analyzed in this paper is primarily done at universities. In addition to the creation of new knowledge, public support of university research helps train both undergraduate and graduate students. These students may become employed in the pharmaceutical industry and may carry with them the research knowledge and experience made possible through public support of their training. Thus, it is not possible to separately identify complementarity due to the disembodied spillover of knowledge and complementarity due to the transfer of knowledge by people. Both mechanisms are probably important, and, given improvements in data, future research should try to deconstruct the impact of public research in terms of the spillover components of labor and pure knowledge.

Appendix

Data Construction

Proxies for public basic and clinical research investment were created by use of the CRISP database, which is maintained by the NIH. This database contains

information on extramural and intramural biomedical research grant and contract awards by the NIH and other governmental agencies under the authority of the U.S. Public Health Service (these other agencies include the Food and Drug Administration, the Centers for Disease Control and Prevention [CDC], the Agency for Health Care Policy and Research, and so on). For each grant and contract, the database contains a record identification, the investigator name, title of project, narrative description of project, organization receiving the award and its address, the administrative branch of the NIH or other agency, award amount, type of award, fiscal year of award, city, and state. By use of a second administrative NIH database, called Information for Management, Planning, Analysis, and Coordination (IMPAC), CRISP records were supplemented to include the scientific review group that recommended approval. A scientific review group is a committee of peers within a scientific field that review grant applications and recommend applications to the National Advisory Councils for approval.

Identification of relevant research took place in two stages. The first stage separated all awards into three groups (mixed, clinical, or other) by use of the "type of award code" field (for example, code R01 for a traditional research award or code K08 for a clinical investigator award). A second step in this stage involved sorting the mixed group to identify any remaining clinical or other awards, by use of keyword searches of the grant and contract titles. This step finalized the division into the basic, clinical, and other groups. The second stage separated the basic and clinical groups into seven therapeutic classes and a general category. This was done in five steps. First, awards by agencies that do not fund basic or clinical research relevant to the pharmaceutical industry were eliminated. This eliminated organizations such as the CDC, the National Library of Medicine, the National Institute of Nursing Research, and so on. Second, scientific review groups were matched to their corresponding therapeutic classes. Third, keyword filters were used to further sort those grants and contracts not matched by scientific review group. Fourth, the remaining uncategorized grants and contracts were allocated to therapeutic classes by use of NIH codes. For instance, the remaining grants by the National Cancer Institute were included in the endocrine/cancer class, and the remaining grants by the National Eye Institute were included in the central nervous system class. Fifth, for those NIH divisions that are too general for classification, such as the National Institute of General Medicine, the grants and contracts were allocated across the seven classes in the proportion of those successfully categorized.

The process resulted in seven public basic research flows and seven public clinical research flows for every year in the CRISP database (1972–96). These flows were deflated by use of the NIH Biomedical Research and Development Price Index maintained by the Bureau of Labor Statistics (base year of 2000).

References

Abel, Andrew B., Avinash K. Dixit, Janice C. Eberly, and Robert S. Pindyck. 1996. Options, the Value of Capital, and Investment. *Quarterly Journal of Economics* 111:753–77.

American Association for the Advancement of Science. 2006. NIH Budget Remains Flat in 2007. http://www.aaas.org/spp/rd/nih07p.pdf.

Arora, Ashish, and Alfonso Gambardella. 1994. Evaluating Technological Information and Utilizing It. *Journal of Economic Behavior and Organization* 24:91–114.

Carruth, Alan, Andy Dickerson, and Andrew Henley. 2000. What Do We Know about Investment under Uncertainty? *Journal of Economic Surveys* 14:119–53.

Cockburn, Iain M., and Rebecca M. Henderson. 1997. Public-Private Interaction and the Productivity of Pharmaceutical Research. Working Paper No. 6018. National Bureau of Economic Research, Cambridge, Mass.

———. 2001. Publicly Funded Science and the Productivity of the Pharmaceutical Industry. *Innovation Policy and the Economy* 1:1–34.

Cohen, Wesley M., and D. A. Levinthal. 1989. Innovation and Learning: The Two Faces of R&D. *Economic Journal* 99:569–96.

Cohen, Wesley M., Richard R. Nelson, and John P. Walsh. 2002. Links and Impacts: The Influence of Public Research on Industrial R&D. *Management Science* 48:1–23.

Colyvas, Jeannette, Michael Crow, Annetine Gelijns, Roberto Mazzoleni, Richard R. Nelson, Nathan Rosenberg, and Bhaven N. Sampat. 2002. How Do University Inventions Get into Practice? *Management Science* 48:61–72.

David, Paul A., and Bronwyn H. Hall. 2000. Heart of Darkness: Modeling Public-Private Funding Interactions inside the R&D Black Box. *Research Policy* 29:1165–83.

David, Paul A., Bronwyn H. Hall, and Andrew A. Toole. 2000. Is Public R&D a Complement or Substitute for Private R&D? A Review of the Econometric Evidence. *Research Policy* 29:497–529.

Dixit, Avinash K. 1992. Investment and Hysteresis. *Journal of Economic Perspectives* 6: 107–32.

Dixit, Avinash K., and Robert S. Pindyck. 1994. *Investment under Uncertainty*. Princeton, N.J.: Princeton University Press.

Flowers, Christopher R., and Kenneth L. Melmon. 1997. Clinical Investigators as Critical Determinants in Pharmaceutical Innovation. *Nature Medicine* 3:136–43.

Gambardella, Alfonso. 1995. *Science and Innovation: The U.S. Pharmaceutical Industry in the 1980s.* Cambridge, Mass.: Cambridge University Press.

Gelijns, Annetine C., Nathan Rosenberg, and Alan J. Moskowitz. 1998. Capturing the Unexpected Benefits of Medical Research. *New England Journal of Medicine* 339:693–98.

Giaccotto, Carmelo, Rexford E. Santerre, and John A. Vernon. 2005. Drug Prices and Research and Development Investment Behavior in the Pharmaceutical Industry. *Journal of Law and Economics* 48:195–214.

Grabowski, Henry G., and John Vernon. 1980. The Determinants of Research and Development Expenditures in the Pharmaceutical Industry. Pp. 3–20 in *Drugs and Health,* edited by Robert B. Helms. Washington, D.C.: AEI Press.

———. 2000. The Determinants of Pharmaceutical Research and Development Expenditures. *Journal of Evolutionary Economics* 10:201–15.

Guellec, Dominique, and Bruno van Pottelsberghe. 2003. The Impact of Public R&D Expenditure on Business R&D. *Economics of Innovation and New Technology* 12:225–44.

Hall, Bronwyn. Forthcoming. The Financing of Innovation. In *Handbook of Technology and Innovation Management,* edited by Scott Shane. Oxford: Blackwell Publishers.

Hall, Bronwyn H., Zvi Griliches, and Jerry A. Hausman. 1986. Patents and R&D: Is There a Lag? *International Economic Review* 27:265–83.

Henderson, Rebecca, and Iain M. Cockburn. 1996. The Determinants of Research Productivity in Ethical Drug Discovery. Pp. 167–93 in *Competitive Strategies in the Pharmaceutical Industry,* edited by Robert B. Helms. Washington D.C.: AEI Press.

Hubbard, R. Glenn. 1998. Capital Market Imperfections and Investment. *Journal of Economic Literature*, 36:193–225.

Jaffe, Adam B. 1989. The Real Effects of Academic Research. *American Economic Review* 79:957–70.

Maxwell, Robert A., and Shohreh Eckhardt. 1990. *Drug Discovery: A Case Book and Analysis.* Clifton, N.J.: Humana Press.

NIH (National Institutes of Health). Office of the Director. 1997. The NIH Director's Panel on Clinical Research: Report to the Advisory Committee to the NIH Director. http://www.nih.gov/news/crp/97report/execsum.htm.

———. Office of Science Policy. 2000. NIH Contributions to Pharmaceutical Development: Case Study Analysis of the Top-Selling Drugs. Appendix C in *Rx R&D Myths: The Case against the Drug Industry's R&D "Scare Card."* Washington, D.C.: Public Citizen, Congress Watch.

PhRMA (Pharmaceutical Research and Manufacturers of America). 1980–99. Annual Survey Report. Washington, D.C.: PhRMA.

Pindyck, Robert S. 1991. Irreversibility, Uncertainty, and Investment. *Journal of Economic Literature* 29:1110–48.

Reichert, Janice M., and Christopher-Paul Milne. 2002. Public and Private Sector Contributions to the Discovery and Development of 'Impact' Drugs. *American Journal of Therapeutics* 9:943–55.

Scherer, Frederic M. 1996. Commentary on Part Three. Pp. 269–73 in *Competitive Strategies in the Pharmaceutical Industry,* edited by Robert B. Helms. Washington, D.C.: AEI Press.

———. 2001. The Link between Gross Profitability and Pharmaceutical R&D Spending. *Health Affairs* 20:216–20.

U.S. Congress. Office of Technology Assessment. 1993. *Pharmaceutical R&D: Costs, Risks and Rewards.* Washington, D.C.: Government Printing Office.

U.S. Department of Health and Human Services. National Center for Health Statistics. 2004. *International Classification of Diseases, Ninth Revision, Clinical Modification.* Washington, D.C.: Government Printing Office.

Vernon, John A. 2005. Examining the Link between Price Regulation and Pharmaceutical R&D Investment. *Health Economics* 14:1–16.

Ward, Michael R., and David Dranove. 1995. The Vertical Chain of Research and Development in the Pharmaceutical Industry. *Economic Inquiry* 33:70–87.

Wiggins, Steven N. 1983. The Impact of Regulation on Pharmaceutical Research Expenditures: A Dynamic Approach. *Economic Inquiry* 21:115–28.