The Changing Structure Of The Pharmaceutical Industry

Drug development under today's new institutional arrangements could turn out to be faster and better, but not cheaper.

by Iain M. Cockburn

ABSTRACT: Rising research and development (R&D) expenditures by pharmaceutical companies are, in part, a consequence of changing industry structure, particularly the rise of the biotechnology sector. The creation of a market for biomedical science and increased vertical competition within the industry are likely to spur innovation and raise productivity, but they also could induce socially wasteful spending and weaken academic science. With innovation increasingly dependent on financially vulnerable firms and complex contractual arrangements, R&D investment might be becoming more sensitive to price controls or other cost containment measures.

BY SOME ACCOUNTS, the pharmaceutical industry is facing a productivity crisis. Notwithstanding extraordinary scientific achievements such as completing the sequencing of the human genome, the rate at which the industry generates new products appears to be shrinking. In 2002 the U.S. Food and Drug Administration (FDA) approved only seventeen new molecular entities (NMEs) for sale in the United States—a disappointing fraction of the fifteen-year high of fifty-six NMEs approved in 1996 and the lowest since 1983. Alarmingly, this decline occurred despite a doubling of research and development (R&D) spending by U.S.-based pharmaceutical companies between 1995 and 2002 (Exhibit 1). The same pattern is apparent in worldwide statistics, where the annual number of new active substances approved in major markets fell by 50 percent during the 1990s, while private-sector pharmaceutical R&D spending tripled.[1] These numbers have prompted headlines about "dry," "weak," or "strangled" pipelines and claims that "Big Pharma's business model is bankrupt."

These concerns are almost surely overblown. Underlying trends in R&D productivity are difficult to extract from these indicators, and the apparent decline they suggest could be partly, if not entirely, a mirage. "True" research productivity, in the sense of the relationship between current R&D spending and the stream of future benefits attributable to it, is difficult to measure. The trends in Exhibit 1 illustrate this point, showing two widely watched indicators of industrial pharmaceutical research input and output during 1970–2002.

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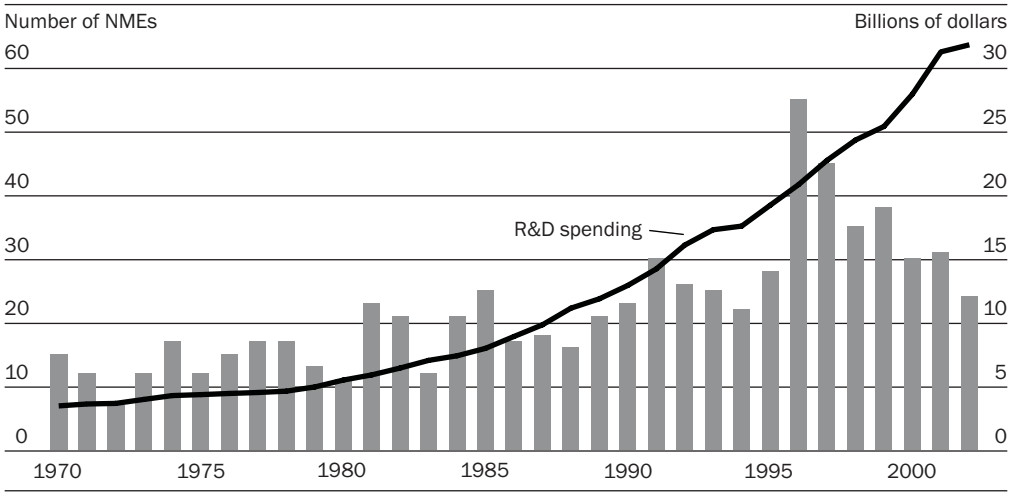
DOI 10.1377/hlthaff.23.1.10

EXHIBIT 1
Pharmaceutical Research And Development Trends In The United States, 1970–2002



SOURCES: For number of new molecular entities (NMEs) approved, U.S. Food and Drug Administration, Center for Drug Evaluation and Research. For PhRMA members' spending, Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile, 2002* (Washington: PhRMA, 2003).
NOTE: Line relates to the right *y* axis and denotes worldwide research and development (R&D) spending by PhRMA member companies, inflation-adjusted to constant 2002 dollars by the National Institutes of Health (NIH) Biomedical R&D price deflator.

On the output side, counts of NMEs are a noisy measure. On average, over the long term, these numbers have been remarkably steady, but they fluctuate sharply from year to year, so that peak-to-trough changes over shorter time periods can be highly misleading. Also, depending on how they are constructed, counts of NMEs might exclude large-molecule drugs, vaccines, and other biologics.[2] Most importantly, these counts do not weigh the medical or economic significance of different molecules; if the average "quality" of NMEs has been improving over time, these numbers will understate true research output.

On the input side, several factors frustrate accurate counting. Since the costs of doing R&D have been rising rapidly, increases in nominal R&D spending likely overstate the real increase in resources applied to drug discovery and development. Also, the long, complex process of drug development makes it remarkably difficult to fully account for and unambiguously attribute specific inputs to specific outputs.[3] Today's new drugs are the product of yesterday's R&D spending, and today's R&D spending will contribute to output far in the future.

Moreover, by most indicators the pipeline of drugs in development is full; by one measure, 3,200 new drug candidates have entered it in the past twenty-four months alone.[4] If experience is any guide, the recent surge in R&D spending should therefore generate a commensurate increase in new drugs over the next three to ten years. Skepticism about what can be learned from easily observable statistics should not, however, distract us from the imperative to understand research productivity and its sensitivity to policy changes. The level of resources

committed to medical research is breathtaking: By one estimate, $75 billion was spent on global health care R&D in 1998, much of it on pharmaceuticals and supporting science and technology, and this figure probably now exceeds $100 billion per year.[5] Since there is an opportunity cost attached to these resources, "bang for the buck" is a serious concern. Pharmaceutical R&D has paid off handsomely in previous decades, with statistical studies showing a historical correlation between the number of new drugs introduced and declines in mortality and other health indicators across a wide range of diseases.[6] Nonetheless, progress has been disappointing in some areas: No new broad-spectrum antibiotics have been marketed in almost forty years, and many forms of cancer as well as chronic diseases such as diabetes, Alzheimer's, Parkinson's, and schizophrenia still lack effective, well-tolerated treatments. Continuing growth in R&D spending represents investment in overcoming these challenges, but this upward trajectory will be sustainable only if it can be paid for. As increased spending collides with intensifying pressure to contain health care costs, the factors driving the efficiency of the drug discovery and development process are being brought into sharp focus.

Why Is R&D Spending Increasing?

Some of the factors driving higher R&D spending are good news from a productivity perspective. Much of the increase is a response to the vastly expanded research opportunities created by advances in basic science. The number of drug targets has risen from 500 to more than 5,000 in recent years, and expansion of research activity to investigate them is a natural and desirable consequence. Some part of the spending increase also represents well-justified "retooling" investments in new technology and development of new research capabilities that will pay off for years to come. But other spending drivers might be lowering industry productivity. Two much-discussed issues are "mining out" and regulatory delay. Research might necessarily be becoming more expensive because the "low-hanging fruit" has been already been picked: Current areas of unmet medical need are increasingly those in which diseases are more complex and more difficult to understand and control, and drug targets more difficult to attack. And notwithstanding various reforms of the funding and management of the FDA, the time and cost of obtaining regulatory approval remain sources of concern.

Less attention, however, has been paid to the consequences of changing industry structure, which is the focus of this essay. For an individual drug company, productivity is the rate at which new drugs are produced relative to the rate of R&D spending. This in turn is a function of "shots on goal"—that is, the number of lead compounds generated or acquired, the probability of their making it through preclinical and clinical development phases, and how long this takes. Technological developments such as combinatorial chemistry, rapid-throughput screening, microfluidics, bioinformatics, and so on have made parts of this process much more efficient. In addition, academic studies have shown that at least in the

1980s, productivity was also related to the size and diversity of the company's research effort, its reward systems, and the nature of internal decision making and distribution of authority.[7] Progress in these areas has raised research productivity at the firm level, but the performance of a single firm cannot be understood in isolation. Overall "system" productivity of the industry as a whole—understood to include for-profit companies, philanthropic institutions, government labs, and academic science and medicine—is a function of both the efficiency of its component institutions and the ways in which they interact.

The organization of the industry—numbers and types of institutions, allocation of effort among them, and relationships between them—has seen some profound changes over the past thirty years. Many smaller firms have disappeared as leading players have consolidated, while vigorous biotechnology-based competitors have entered the industry. Perhaps most important, relationships between nonprofit and for-profit sectors have changed dramatically, with an entirely new industry segment—the biotechnology "tool" companies—emerging at the interface between academic and commercial research.

The overall impact of this "vertical dis-integration" on R&D spending and industry productivity is far from clear. There are good reasons to believe that it could result in dramatically improved productivity over the long term. But there are also good reasons to believe that these changes could be inducing unproductive and socially wasteful R&D spending and transforming the nature of academic biomedical research in ways that may have a negative effect on system performance. Surprisingly little evidence is available on the key issues, and, sadly, the remainder of this essay raises many more questions than it answers.

The Evolution Of Industry Structure

■ **Until 1980: upstream open science, downstream "Big Pharma."** Under the industry structure that prevailed until the mid-1970s, for-profit firms were almost all large enterprises, fully integrated from drug discovery through clinical development, regulatory affairs, manufacturing, and marketing. Most commercial drug discovery was conducted in house and, at least in the early part of this period, was dominated by large-scale "random screening" programs with limited requirements for deep knowledge about fundamental physiological processes. Licensing activity was driven largely by downstream concerns: Rights to sell drugs that were already approved (or in the late stages of clinical development) would be acquired, to maintain efficient levels of use of manufacturing or marketing assets or, in the international context, to take advantage of local knowledge and access to regulators and distribution channels. Upstream technology was largely acquired either "for free" by reading journals and attending conferences or by purchasing tangible inputs and services, such as scientific instruments or highly skilled graduates.

Pharmaceutical companies appropriated returns from R&D through a combination of extensive patenting, proprietary know-how, brands, regulatory barriers

to entry, and favorable product market conditions. Most of these firms were long-lived, mature organizations, tracing their roots back many decades, often to the nineteenth century chemical industry. Their large and sustained investments in R&D, marketing assets, and human and organizational capital were largely financed from internal cash flow. Competitive advantage was driven by firms' ability to effectively manage product market interactions with regulators and end users and to "fill the pipeline" with internally developed blockbuster drugs. In turn, the productivity of internal R&D appears to have been driven by economies of scale and scope in conducting research, efficient allocation of resources in internal capital markets, and the ability to capture internally and externally generated knowledge spillovers.

In the upstream not-for-profit sector, taxpayers (and to some extent philanthropists) supported curiosity-driven research conducted at cottage industry scale inside government labs, universities, research institutes, and teaching hospitals. Legal constraints and a strong set of social norms limited commercial or contractual contacts between drug companies and the world of "open science." Resource allocation in the not-for-profit sector was driven by peer-reviewed competition for grants on the basis of scientific merit and the reputation of individual researchers. The importance of establishing priority and reputation drove early and extensive publication of results, and social norms (and requirements of granting agencies) promoted routine sharing of research materials. Not-for-profit researchers concentrated largely on basic science and filed few patents.[8]

This is, of course, a gross oversimplification. Many drug companies invested sizable resources in "blue sky" basic research, and specialist research boutiques sold technology to large firms. Public-sector institutions conducted screening programs for drug candidates, and many academic researchers had close financial and contractual links with drug companies through individual consulting arrangements as well as institutional research grants and contracts. Funding priorities reflected political pressure, intellectual fashions, and the dynamics of the "Matthew Effect," as well as pure scientific merit.[9] Importantly, the "waterfall" notion of vertical knowledge spillovers—with a one-way flow of ideas down a gradient running from upstream basic science to downstream applied research and clinical practice—was only partially true in this era. Nobel-winning work in basic science was done in for-profit labs, and nonprofit institutions were an important source of data, techniques, and expertise in late-stage drug development, epidemiology, and postmarketing follow-up. There was much movement of ideas, candidate molecules, research materials, and researchers back and forth across the for-profit/not-for-profit divide. The vertical structure of the industry prior to 1980 can nonetheless be characterized as being essentially binary, with a clear distinction drawn between upstream open science and a downstream commercial sector dominated by "Big Pharma"—about forty large, highly integrated firms.

■ **1980 and beyond: growing complexity.** By contrast, in recent years industry

structure has become much more complex. After decades of stability and consolidation, in the 1980s the for-profit side of the industry experienced significant entry from biotechnology companies, many of which positioned themselves as an intermediate sector between academic research institutions and Big Pharma. By the mid-1990s several thousand biotech ventures had been launched, and several hundred had reached sufficient scale to be an important force in the industry. Existing vertical relationships were disrupted and reformed, with the new companies straddling (and blurring) the divide between for-profit and not-for-profit research. Although most were overtly profit oriented, they also had much tighter personal, geographical, cultural, and contractual links to nonprofit research institutions. Academic scientists played a particularly important role in the founding of these companies, either moving out of academic employment or participating actively in both worlds.[10] While some of the new companies sought to be fully integrated horizontal competitors with Big Pharma, and a handful succeeded in doing so, most assumed the role of specialist suppliers of leading-edge technology to downstream firms.

Several interlinked technological, economic, and legal forces appear to have brought about this change. Revolutionary scientific discoveries in the 1970s, such as gene splicing and the ability to create monoclonal antibodies, opened up new areas of research, and the pace of discovery in basic biomedical science accelerated dramatically in subsequent decades, raising the importance of close contact with university science. At the same time, developments in patent law brought much of molecular biology and the life sciences within the ambit of the patent system. Without patent rights in inventions in areas such as isolation and purification of proteins, DNA sequences, monoclonal antibodies, knockout and transgenic organisms, gene expression systems, and so on (or at least the prospect of obtaining and enforcing them), many biotech companies would never have been founded. Other important policy changes include the passage of the Bayh-Dole Act, which relaxed barriers to licensing of government-sponsored research, and changes in tax and financial regulations, which brought about a venture capital industry (and ultimately a stock market) that was willing to support inexperienced companies entering a market with a seven-to-ten-year product development cycle.[11] At least in the U.S. equity markets, tolerance for risk has risen, and after a few well-hyped early successes, investors became comfortable with the idea of "high science for profit," developed a shared language and conceptual framework for valuing these new ventures, and—periodically—have been willing to support the new sector with substantial injections of capital.

The revolution in life sciences also affected organizational and managerial aspects of drug research. As drug discovery became more science-intensive, with increased emphasis on "deep" understanding of physiology at the molecular level, it became not just more expensive but also more difficult to manage. As "rational drug design" took center stage, changes in the nature of research activity were accompanied by complementary changes in the internal structure of commercial

R&D organizations. Drug companies began to look and behave more like universities, with increasing emphasis on collaboration, publication, and exchange of (precompetitive) information.[12] This was accompanied by increased willingness to exploit external sources of technology, through in-licensing or strategic partnerships. In this environment, specialist research firms could expect at least to survive, if not to prosper. At the same time, the growing cost and complexity of academic research projects forced successful scientists to acquire managerial and organizational skills—leaving them better equipped to run business ventures and looking much more like entrepreneurs and managers to outside investors or business partners. As rising costs and growing societal pressure to justify their budgets pushed universities and other publicly funded institutions to become more tolerant of "just-off-campus" commercial activity, or even to actively encourage it, this cadre of scientist-entrepreneurs was well positioned to take advantage of the commercial opportunities their research created.

By 1990 it was clear that biotechnology was here to stay. Although investors' interest waxes and wanes, fresh waves of entrants have been able to take advantage of periodic opening of the financing window, and the pharmaceutical industry has developed a new vertical structure, with biotech "tool" companies as a specialized layer between Big Pharma and the nonprofit sector. Big Pharma now increasingly relies on the research tools and product leads provided by biotechs, and 25–40 percent of its sales are reported to come from drugs that originated in the biotech sector.[13] The orderly world of the "waterfall model" has been replaced by one in which information and materials circulate rapidly between not-for-profits, Big Pharma, and the biotechs, supported by a complex set of contractual agreements and collaborative arrangements.

Is The New Industry Structure More Efficient?

Most economists believe that profit-seeking market outcomes tend to be socially optimal and that more clearly defined property rights, more competition (particularly from entrepreneurial ventures), and more use of prices to guide decisions will generate more efficient allocation of resources. To the extent that the new industry structure incorporates these features, it is therefore almost by definition likely to be more productive in turning advances in fundamental science into new drugs. But is it obvious that the new industry structure is the most efficient way to organize pharmaceutical research? In thinking about this question, it is worth noting that the major successes of the industry—blockbuster drugs for hypertension, cholesterol, depression, ulcers, and so on—are the results of research done decades ago, under the old binary industry structure.[14] What, indeed, was wrong with that structure? By most measures, productivity of the industry and its component sectors was outstanding. Academic output in the life sciences in the second half of the twentieth century was remarkably high, with major advances made in understanding physiology and the molecular basis of disease. On

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the for-profit side, industry used these advances to create drugs that dramatically reduced mortality, human suffering, the economic burden of illness, and treatment costs for many diseases and conditions. Substantial benefits to patients were accompanied by high returns to investors. So what was broken that needed fixing? To what problems was dis-integration of the industry the solution?

■ **Reasons to like upstream competition.** Efficiency gains from specialization, market-driven resource allocation, and intensified competition could well be substantial.[15] First, although large, integrated firms minimize some costs, they also could raise others. Gains from vertical integration come at the cost of creating internal bureaucracies to coordinate activity, which are costly to maintain and could cause rigidity, organizational "slack," and a bias toward conservative decisions—limiting these firms' ability to respond to new technological opportunities. It is widely believed that new enterprises are therefore faster and more cost-effective at developing new technologies. Specialization and "focus," and the high-powered incentives faced by employees of entrepreneurial companies, probably give the new entrants major cost advantages in doing certain kinds of research.

Second, large incumbent firms could slow down technological progress. Incumbents might have incentives to shelve or abandon new technologies, to avoid cannibalizing their existing products. Interestingly, limiting proprietary rights in early-stage technologies can reinforce incumbents' competitive position. Indeed, incumbents sometimes take actions on their own to limit intellectual property in new technologies. The "Strategy of the Commons" argument suggests, for example, that by putting new technology in the public domain, incumbent firms can deter entry into their markets.[16] By denying entrants the ability to establish patent rights, their ability to raise capital and establish a proprietary market position is sharply limited. Indeed, the Single Nucleotide Polymorphisms (SNP) consortium, which was sponsored by Big Pharma to put key genomic information in the public domain, has been suggested as an example of this dynamic in action.

Third, supporting a market in basic biomedical research through tax policy, rules governing public research funding, and, most importantly, allowing strong, broad patents on upstream technology could speed up the progress of science. Development of basic technologies in secret is socially costly. If scientific advances and research data are generated inside vertically integrated firms and held as trade secrets, knowledge spillovers and social returns are likely to be lower than if they are disclosed in patent applications. The prospect of obtaining broad patent rights in early-stage technologies could stimulate socially valuable investment in R&D, as well as further rapid innovation as second movers invent around the first set of patents on a new technology. Models of sequential innovation highlight the im-

portance of balancing the division of returns between first and second movers for equilibrium levels of R&D, and being too reluctant to grant strong rights to early innovators could therefore have deleterious effects.[17] Although the "gold rush" and "land grab" metaphors often used to describe genome patenting raise the specter of socially wasteful rent dissipation, such racing behavior could also have beneficial effects. Competitive races finish faster. Falling behind in a protracted race could cause weak competitors to drop out, weeding out bad ideas or poorly conceived enterprises. Game theoretic modeling of technology races suggests that in some circumstances social returns can be raised by awarding patents early rather than late in the development of a technology.[18]

■ **Reasons to discourage upstream competition.** Enthusiasm about the potential productivity advantages of upstream entrants should, however, be tempered by the recognition that large, vertically integrated firms are an efficient response to some serious real-world problems. These include difficulties in managing risk where capital markets are imperfect, difficulties in writing workable contracts on upstream technology, the inability to effectively capture knowledge spillovers, and a variety of problems that arise from flaws in markets for information. In fact, there is a strong presumption that vertically integrated firms are the first best solution to problems such as financing and management of multiple projects that are long-term, risky, and complex; involve activities that are costly to monitor; require substantial project-specific unrecoverable investments; and have shared costs and vertically complementary outcomes—that is, pharmaceutical R&D!

The new industry structure also could induce behavior that reduces system productivity. First, the expansion of research opportunities could have induced R&D spending that is wasteful from a societal perspective. The winner-takes-all prospect of obtaining broad upstream patent rights over genomic information and fundamental biological mechanisms could have induced "racing" behavior by both Big Pharma and the biotechs, with scarce resources being dissipated in an effort to outpace rivals. Downstream companies face a strategic imperative to make purely defensive investments in intellectual property and internal research capabilities to strengthen their bargaining position with respect to upstream players. (All else being equal, in negotiations over access to new technology, better terms will be obtained by a prospective licensee with a credible threat to invent around the licensor's patent, or patents of its own to counterassert against the licensor.)

Second, some of the increase in R&D spending represents payments for access to upstream science of the kind that used to be obtained "for free" by downstream institutions in the form of knowledge spillovers but is now explicitly priced in the form of license agreements and research collaborations between Big Pharma and universities and biotech companies. These payments do not necessarily represent unproductive use of resources—indeed, they could in fact induce faster and more effective creation and transfer of knowledge, and raise rather than lower system productivity—but the substitution of this market for biomedical science for the

old arrangements raises some interesting questions.

Consider the stylized case of a biotech tool company that holds a valid, enforceable patent on gene coding for a target, whose claims will be infringed by any attempt by a downstream drug company to develop a marketable drug for that target. The drug company, in turn, blocks access to the end user with its own product or use patents. The logic of the "double-marginalization problem" dictates that instead of having the tool company charge a monopoly price to the pharmaceutical company, which then independently determines a price for the final product based on end-user demand and (now higher) marginal costs, the two parties should agree on an end-user price that maximizes joint profit, then divide it. The classic question is whether the two parties can agree on a division of surplus, and whether bargaining costs will eat up any efficiency gains.

Bargaining is likely to be easy and efficient when both participants can agree on the payoff, neither has an informational advantage, and both are equally risk-averse. However, in this context these assumptions are violated, and it is quite likely that the two firms will find it hard to agree. The tool company will tend to have overinflated expectations of the value it brings to the table, while the drug company will be in a stronger bargaining position given its greater size, wider range of other opportunities, and ability to credibly threaten to invent around the tool company's patent (or litigate it to death). Both sides will likely have plenty of private information (the drug company will be better informed about market prospects and product development risks, while the tool company will be better informed about its technology), and incentives to act opportunistically on it, raising the costs of drawing up a contract that protects both parties' interests and inducing them to make defensive investments.

To cap it all, imperfect capital markets mean that this tool company will periodically be facing a very real threat of bankruptcy. When the funding window is closed, cash-poor companies are easily pressured into entering agreements on adverse terms: a low fixed fee rather than a high reachthrough royalty rate, plus exclusivity provisions that limit its ability to sell its technology elsewhere or exploit it through internal development. Add a little more realism to this picture by introducing the costs of coordinating contracts with multiple tool vendors, difficulties in reaching agreement at all where there are multiple competing patent positions, and uncertainty about the ultimate validity and enforceability of broadly written patents, and it becomes increasingly difficult to be optimistic about efficient outcomes' being reached in licensing negotiations.[19]

As this example suggests, upstream competition might be reducing value creation in the industry through waste of resources on bargaining and other transaction costs. Another, more subtle, problem is that prices in the market for upstream technologies might have been greatly distorted by informational asymmetries, thin markets, bad bargaining outcomes, and other problems. Using market prices as signals for resource allocation works well from a social perspective when prices

reflect the marginal opportunity cost of the resources employed. But when market failure drives a wedge between prices and marginal opportunity costs, markets send the wrong signals, and poor decisions result.

Finally, pushing the boundary between open science and for-profit research further upstream could be undermining academic research—a vital but fragile component of the biomedical innovation system. Historically, academic research has been driven by social norms and resource allocation procedures that ignored market signals and commercial concerns. Further extension of property rights into the domain of academic research could result in decreased information sharing and increased emphasis on product market potential over scientific merit in funding decisions and priorities of individual researchers, with serious long-term consequences for the future vitality and productivity of fundamental science.[20]

Concluding Thoughts

Vertically disaggregated industries are not necessarily inefficient, and specialized research firms can play an important role in the right circumstances. In general, one can be optimistic about efficiency being raised by increased vertical specialization in industries where competition is high among horizontal segments, where specialization reduces costs, where vertical coordination is relatively unimportant, where prices for the upstream technology accurately reflect marginal opportunity costs, and where bargaining and contracting are easy and effective.

Is this the case in early-stage pharmaceutical research? Several aspects of the economic relationship between biotech tool companies and Big Pharma suggest otherwise. Muted price signals from end users, high levels of uncertainty, high transaction costs and serious contracting problems, and limited competition in specific areas of technology all make finding an efficient vertically dis-integrated solution less likely. (In contrast, horizontal competition with Big Pharma from product-oriented biotechs will likely have a socially beneficial effect.) If this is the case, then further vertical restructuring induced by regulatory or technological change could have adverse effects on the productivity of the industry. For example, "more and stronger patents" could make things worse if they induce excess entry upstream or exacerbate contracting problems.

For economists, excess entry, high failure rates, and the inability to make profits are signs of overinvestment, "wrong prices," and misallocation of resources. Anecdotal evidence and the relatively low average stock market returns from biotechnology companies over the past few decades support this pessimistic view. Entrepreneurial energy and strong patent positions have not, thus far, allowed the biotech sector to gain a sizable share of industry profits. This reflects in part the superior bargaining position of the downstream firms, which have largely been able to dictate contractual terms. But it also reflects what Richard Nelson called "the simple economics of basic scientific research"—patents or no patents, capturing the value that ultimately derives from fundamental research is extraordi-

narily difficult for profit-oriented organizations. Historically, the firms that have succeeded in doing this have been large, stable, and highly integrated, sufficiently diversified in product markets to capture spillovers and financially strong enough to be able to effectively manage risk internally.

There is a genuine possibility, therefore, that the restructuring of the pharmaceutical industry will ultimately prove quite costly in terms of lower productivity. Drug development under the new set of institutional arrangements might turn out to be faster and better, but not cheaper. Resources burned up in the vertical struggle for profits in the industry, or wastefully overinvested in unviable enterprises, might be a significant offset to those saved through superior research tools and competitive pressure to be efficient. Of course, these extra costs could be worth incurring if the technological opportunities opened up by recent scientific advances are realized. The rise of the biotech sector might ultimately generate even larger social returns than those attributable to a similar surge of entrepreneurship, technological dynamism, and industry restructuring in the computer business during the transition from the era of mainframes. But in the meantime, the industry is in a particularly vulnerable position. System productivity is increasingly dependent on Big Pharma's ability to support academic and for-profit research through commercial relationships, which could be the first to break down if price regulation or changes to third-party payer arrangements subject the industry to a profit squeeze.

Unfortunately, given delays of several decades between performing basic science and measurable impacts on human health, unambiguous evidence on these issues will take a long time to accumulate. Thirty years after the dawn of the biotech industry, when one is called upon to the assess the impact of changing industry structure on research productivity, the prudent response is to repeat Chou En-Lai's reply when asked by Henry Kissinger to comment on the impact of the French Revolution: "Too early to tell."

The views expressed are solely those of the author.

NOTES

1. EFPIA member companies spent $47 billion in 2002. European Federation of Pharmaceutical Industries and Associations, *The Pharmaceutical Industry in Figures, 2003 Update* (Brussels: EFPIA, 2003).
2. Seven new biotech drugs and vaccines were approved in both 2001 and 2002, up from one or two per year in the early 1990s. U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, www. fda.gov/cber/products.htm (22 October 2003).
3. Joseph DiMasi and colleagues at the Tufts Center for the Study of Drug Development used proprietary company data to calculate the cost per approved NDA, taking into account failed projects and opportunity cost of money committed to lengthy development processes. Based on their calculations, the cost in constant dollars per approved drug rose from $318 million in the late 1980s to $802 million over the following thirteen years. See J. DiMasi et al., "Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics* 10, no. 2 (1991): 107–142; and J. DiMasi et al., "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22, no. 2 (2003): 151–185.
4. *Pharmaprojects Annual Review, 2003* (London: PJB Publications, 2003).
5. World Health Organization, Global Forum for Health Research, *Monitoring Financial Flows for Health Research*

(Geneva: WHO, 2001).

6. F.R. Lichtenberg "The Impact of New Drug Launches on Longevity: Evidence from Longitudinal, Disease-Level Data from Fifty-two Countries, 1982–2001," NBER Working Paper no. 9754 (Cambridge, Mass.: National Bureau of Economic Research, 2003).
7. R.M. Henderson and I.M. Cockburn, "Measuring Competence: Exploring Firm Effects in Pharmaceutical Research," *Strategic Management Journal* 15 (1994): 63–84; and R.M. Henderson and I.M. Cockburn, "Scale, Scope, and Spillovers: Determinants of Research Productivity in the Pharmaceutical Industry," *RAND Journal of Economics* 27, no. 1 (1996): 32–59.
8. See R. Landau, B. Achilladelis, and A. Scriabine, eds., *Pharmaceutical Innovation* (Philadelphia: Chemical Heritage Press, 1999); and R.A. Maxwell and S.B. Eckhardt, *Drug Discovery: A Case Book and Analysis* (Clifton, N.J.: Humana Press, 1990).
9. "For whosoever hath, to him shall be given, and he shall have more abundance," Matt. 12:13. The "Matthew Effect" means that established researchers have greater success in obtaining resources than do younger colleagues with untested ideas. See R.K. Merton, "The Matthew Effect in Science," *Science* 159 (1968): 56.
10. L. Zucker, M. Darby, and M. Brewer, "Intellectual Human Capital and the Birth of U.S. Biotechnology Enterprises," *American Economic Review* 88, no. 1 (1998): 290–306.
11. The Bayh-Dole Patent and Trademark Amendments Act of 1980 provided blanket permission to apply for patents on results of federally funded research, harmonized an ad hoc system of intellectual property rules that had been negotiated between individual universities and government agencies, and expressed explicit congressional support for universities to negotiate exclusive licenses with corporations for the results of federally funded research. Regarding the regulatory changes, see P. Gompers and J. Lerner, *The Venture Capital Cycle* (Cambridge, Mass.: MIT Press, 1999).
12. I.M. Cockburn and R.M. Henderson, "Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery," *Journal of Industrial Economics* 46, no. 2 (1998): 157–182.
13. CMR International, as cited in EFPIA, *The Pharmaceutical Industry in Figures* (Brussels: EFPIA, 2000).
14. The same observation holds true for earlier major medical discoveries, such as penicillin and cortisone.
15. Salient examples such as Genentech's development of recombinant human insulin, developed remarkably quickly in contrast to the decades taken to bring statins or angiotensin-converting enzyme (ACE) inhibitors to market, suggest that these gains could be very large. But there is little systematic evidence on the relative productivity of biotechs versus Big Pharma or, indeed, on whether breakthrough product development times (from fundamental science to product launch) are any faster or slower since the 1980s.
16. A. Agrawal and L. Garlappi, "Public Sector Science and the Strategy of the Commons (Abridged)," Best Paper Proceedings, Academy of Management, 2002. An interesting variant of this "scorched earth" strategy is to sponsor university research, but only on condition that it be licensed nonexclusively.
17. The theoretical literature on patents stresses the importance of incentives to early-stage inventors for equilibrium rates of technological progress. See S. Scotchmer, "Standing on the Shoulders of Giants: Cumulative Research and the Patent Law," *Journal of Economic Perspectives* 5, no. 1 (1991): 29–41.
18. K. Judd, K. Schmedders, and S. Yeltekin, "Optimal Rules for Patent Races," Discussion Paper no. 1344 (Northwestern University, April 2002).
19. See M.A. Heller and R.S. Eisenberg, "Can Patents Deter Innovation? The Anticommons in Biomedical Research," *Science* 280 (1998): 698–701.
20. See R.S. Eisenberg, "Property Rights and the Norms of Science in Biotechnology Research," *Yale Law Journal* 97 (1987): 177–223; A. Rai, "Regulating Scientific Research: Intellectual Property Rights and the Norms of Science," *Northwestern University Law Review* 77 (1999): 94–129; and the interesting counterargument of S. Kieff, "Facilitating Scientific Research: Intellectual Property Rights and the Norms of Science—A Response to Rai and Eisenberg," *Northwestern University Law Review* 95 (2000): 691.