MERGERS AND INNOVATION

IN THE PHARMACEUTICAL INDUSTRY

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Introduction

Conflicting trends confound the pharmaceutical industry. The productivity of pharmaceutical innovation has declined in recent years, which is one reason why the share of generic products now accounts for nearly 70 percent of all prescriptions filled in the United States.[1] Despite spending on research and development (R&D) by U.S. companies that more than doubled, in current dollars, in the ten years between 1998 and 2008,[2] the number of new molecular entities introduced into U.S. markets has remained relatively stable at between 20 and 30 per year. Between 1970 and 2007, the average number of new entities approved per year was just over 21.[3]

At the same time, the cohort of large companies who are the leading engines of pharmaceutical R&D has become increasingly concentrated. As recently as 1998, the leading eight companies accounted for 36 percent of US industry shipment of pharmaceutical products. By 2002,

[1] Generic Pharmaceutical Association, Press Release of May 7, 2009.
[2] Pharmaceutical Research and Manufacturers of America, *PhRMA Membership Survey*, 2009.
[3] F.M. Scherer, ""Pharmaceutical Innovation," in Bronwyn Hall and Nathan Rosenberg, eds., *Handbook of the Economics of Technological Innovation*, North Holland, 2010, p. 542-3. See also Iain M. Cockburn, "The Changing Structure of the Pharmaceutical Industry," *Health Affairs*, January/February 2004, p. 11.

their share had risen to more than 53 percent.[4] Actually, that figure understates the extent of concentration among research-based companies because it includes between 18 and 24 percent of shipments made by generic product producers.[5]

The concurrent presence of these trends is not sufficient to determine causation. Indeed, causal factors could work both ways. In response to lagging innovation prospects, some companies have sought refuge in mergers and acquisitions to disguise their dwindling prospects[6] or, some claim, to gain R&D synergies. On the other hand, the increased concentration brought on by recent mergers may have contributed to the declining rate of innovation.

In this paper, we consider the second of these causal relationships: the likely impact of the recent merger wave among the largest pharmaceutical companies on the rate of innovation. In other words, have recent mergers, which may have been taken in response to lagging innovation, represented a self-defeating strategy that only made industry outcomes worse?

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[4] US Bureau of the Census, *Concentration Ratios in Manufacturing Industries*, Washington, various years.
[5] Ibid.
[6] Patricia Danzon et al., "Mergers and Acquisitions in the Pharmaceutical Industry," *Managerial and Decision Economics*, August 2007. See also Peter Elkind and Jennifer Reingold, "Inside Pfizer's Palace Coup," *Fortune*, August 15, 2011.

Two recent mergers give these issues considerable prominence: Pfizer's acquisition of Wyeth Laboratories for $68 billion in January 2009, and Merck & Co.'s acquisition of Schering-Plough a few months later for $41 billion. In 2008, Pfizer invested $7.9 billion on pharmaceutical R&D while Wyeth spent $3.4 billion, for a total of $11.3 billion. The combined firm would then account for 29 percent of U.S. pharmaceutical industry spending on R&D and 22 percent of world-wide spending.[7] Furthermore, Merck had spent $4.8 billion on R&D in 2008 and Schering-Plough had spent $3.5 billion, for a total of $8.3 billion. This second merger would then account for 22 percent of U.S. R&D spending and 17 percent world-wide. The two merged entities therefore would thereby account for fully 51 percent of total U.S. industry R&D spending and 39 percent of total world-wide spending.

Under current U.S. antitrust standards, mergers are evaluated in terms of innovation markets as well as product markets. We therefore discuss the concept of an innovation market. Then we shift our attention to the theory of parallel research paths and review relevant prior studies.

[7] Since neither Pfizer nor Wyeth report how much was spent in the United States and how much abroad, we compare these amounts with both totals. According to PhRMA, total US spending by member companies on pharmaceutical R&D in 2008 was $38.4 billion in the United States and $50.3 billion worldwide. Since, however, not all companies world-wide are PhRMA members, the suggested percentages may be overstated

Next, we offer a simulation analysis for insight into the optimal number of research paths at various combinations of research costs and payoffs. We then review the structure of pharmaceutical research and development in order to relate the simulation results to current industry practice. And finally, we draw conclusions as to the likely impact on pharmaceutical innovation of large horizontal mergers.

Product Markets and Innovation Markets

The U.S. Federal Trade Commission evaluated the competitive effects of both mergers described above. In Pfizer-Wyeth, it originally issued a complaint charging a violation of the antitrust laws, but then negotiated a consent order under which the parties agreed to divest their overlapping assets in the area of animal health. In regard to human health markets, however, and specifically for the "market for basic research and innovation," it found no adverse effects on competition.[8]

The Commission followed a similar path in the Merck-Schering Plough merger case. It issued a complaint but then accepted a consent order under which limited asserts were divested. In this case, there was no mention in any

[8] Federal Trade Commission, "Statement of the Federal Trade Commission Concerning Pfizer/Wyeth," FTC File No. 091-0053, p. 3.

public Commission document of the firms' R&D activities, even though they reflect the primary source of competition among large pharmaceutical companies. This omission is not unusual. While the antitrust agencies typically evaluate pricing practices within relevant product markets, they rarely focus on competition in innovation markets.

The concept of an innovation market was articulated in Guidelines issued in 1995 by the U.S. Department of Justice and the Federal Trade Commission. Those guidelines state:

> An innovation market consists of the research and development directed towards particular new or improved goods or processes, and the close substitutes for that research and development.

They continue:

> In assessing the competitive significance of current and likely potential participants in an innovation market, the Agencies will take into account all relevant evidence. When market share data are available and accurately reflect the competitive significance of market participants, the Agencies will include market share data in their assessment…. The Agencies may base the market shares of participants in an innovation market on their shares of identifiable assets or characteristics upon which innovation depends, on shares of research and development, or on shares of a related product.[9]

From this start, a controversy developed. Gilbert and Sunshine, officials at the Antitrust Division of the U.S. Department of Justice at the time, argued that merger

[9] U.S. Department of Justice and Federal Trade Commission, *Antitrust Guidelines for the Licensing of Intellectual Property*, April 6, 1995, Paragraph 3.2.3.

policy should account for "the effect of merger-induced structural changes on the incentives for research and development and the resulting pace of industrial innovation."[10] They suggested examining possible anti-competitive effects resulting from overlapping R&D efforts by the merging firms; or where aggregate R&D might be reduced on account of the merger; or where R&D would be less efficient on account of the merger.[11]

In response, Rapp argued the "lack of connection between concentration and R&D or innovation."[12] There is no basis in fact or theory," he asserted, that "an increase in R&D concentration is likely to reduce the amount of R&D undertaken, … [or that] reducing the amount of R&D is likely to diminish innovation."[13] While acknowledging that R&D represents the principal input into innovation, and that "in theory, more inputs imply more output," Rapp maintained that to be "an inadequate basis for an innovation-oriented merger policy."[14] With this conclusion, moreover, Carlton and Gertner concurred.[15]

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[10] Richard J. Gilbert and Steven C. Sunshine, "Incorporating Dynamic Efficiency Concerns in Merger Analysis: the Use of Innovation Markets." *Antitrust Law Journal*, Vol. 63, Winter 1995, pp. 569, 570.
[11] Ibid., pp. 594-597.
[12] Richard T. Rapp, "The Misapplication of the Innovation Market Approach to Merger Analysis, *Antitrust Law Journal*, Vol. 64, Fall 1995, pp. 19, 26.
[13] Ibid., p. 27.
[14] Ibid., p. 33.
[15] Dennis W. Carlton and Robert H. Gertner, "Intellectual Property, Antitrust, and Strategic Behavior," in Adam Jaffee and Joshua Lerner, eds., *Innovation Policy and the Economy* Vol. 3, MIT Press, 2003, pp. 29-59.

Gilbert and Sunshine responded that "innovation market analysis is simply a tool to aid in the analysis of competitive effects."[16] If product market analysis is designed to achieve consumer gains from lower prices and increased quantities, then analogously, innovation market analysis is relevant for the goal of achieving faster rates of innovation.

Much of this debate centers on the presumption of ignorance as to the impact of competition on innovation. That presumption sets the stage for this paper whose purpose is to evaluate the effect of increased market concentration on innovative output. However, we limit our attention here to the pharmaceutical industry where such issues are particularly relevant.

The Theory of Parallel Paths

Uncertainty is the dominant reality of pharmaceutical research and development just as it is in other R&D domains. The relevant uncertainties are generally of two broad types: uncertainty about whether a given approach or design or molecule will be technically successful, and uncertainty as to the magnitude of the payoffs, contingent

[16] Richard J. Gilbert and Steven C. Sunshine, "The Use of Innovation Markets: A Reply to Hay, Rapp, and Hoermer," *Antitrust Law Journal* Vol. 64, 1995, p. 82.

upon technical success.[17] Both types are relevant for the discussion below.

Pharmaceutical industry representatives often emphasize the first of these dimensions. They assert that for every successful therapeutic agent, hundreds (or even thousands) of agents are investigated and discarded along the way. Furthermore, this uncertainty persists when prospective drugs enter clinical trials, since only about one out of five drugs entering such trials receives U.S. FDA approval and is commercially introduced.[18] An essential element in any research policy is how to confront this high degree of uncertainty. A long-recognized means for coping with uncertainty is supporting parallel (and independent) research paths toward a specific technical objective.[19]

The oldest known example of this approach was the famous British Longitude Prize, announced in 1714, for which numerous individuals competed with proposed technical solutions.[20] Introducing the prize proposal to Parliament, Isaac Newton offered a non-exclusive list of specific technical avenues. The one he considered least promising *ex*

17 Attention to this important distinction was first drawn by Edwin Mansfield and others in *The Production and Application of New Industrial Technology*, Norton: 1977, pp. 22-32.

18 Christopher P. Adams and Van V. Brantner, "Estimating the Cost of New Drug Development: Is it Really $802 million?" *Health Affairs*, Vol. 25, 2006, pp. 402, 422.

19 See the discussion in John P. Walsh et al., "Effects of Research Tool Patents and Licensing on Biomedical Innovation," in Wesley Cohen and Stephen A. Merrill, eds., *Patents in the Knowledge-based Economy,* National Research Council, 2003, pp. 285-340.

20 See Dava Sobel, *Longitude* (New York: Walker, 1995), especially pp. 51-60.

ante was the one that eventually won the prize. Another example is the Manhattan Project of the 1940s, where U.S. authorities supported five different methods of separating the fissionable materials needed for an atomic bomb, with expenditures anticipated at the outset amounting to 0.3 percent of U.S. gross national product in 1942.[21]

Recognizing the advantages of packing transistors into much smaller cubic volumes, the U.S. military services issued a dozen parallel R&D contracts to achieve a solution.[22] None succeeded, but seeing the demand for such a product, two companies, Texas Instruments and Fairchild, invented the important integrated circuit concept. The predecessor company to Fairchild had made numerous unsuccessful efforts to win one of the military contracts supporting its semiconductor miniaturization work.[23]

The explicit and implicit application of parallel path strategies by the U.S. military spurred theoretical work by economists on the subject. The first important contribution was by Richard Nelson, who showed with a specific numerical example for fighter aircraft development that parallel development strategies could yield more

21 See James Phinny Baxter, *Scientists Against Time*, (MIT Press, 1986), pp. 433-436.
22. See F. M. Scherer, *Industry Structure, Strategy, and Public Policy* (New York: HarperCollins, 1996), pp. 204-204.
23. From a conversation of F.M. Scherer with Victor Jones, a member of the Shockley Semiconductor Lab staff and later professor of solid state physics at Harvard University.

advantageous results than a monolithic approach.[24]

Soon thereafter, Peck and Scherer identified parallel R&D paths as one element of a broader time-cost tradeoff problem in weapons development.[25] The essence of this strategy was

> operating simultaneously two or more approaches to the step, test, or problem to insure that at least one approach will hit the mark at the earliest possible moment.[26]

Peck and Scherer showed that the deeper was the stream of benefits flowing from successful development, the greater the support for a strategy of time-reducing parallel paths.[27] They pointed out that R&D is an investment seeking to yield a stream of benefits in the future, so that pursuing more sequential approaches to development planning often leads to foregone payoffs during the period of probable delay.

In a 1966 article, Scherer extended that analysis by exploring various combinations of parallel and sequential R&D project scheduling alternatives, finding that a convex time-cost tradeoff set persisted over a broad range of

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24 Richard R. Nelson, "Uncertainty, Learning, and the Economics of Parallel Research and Development," *Review of Economics and Statistics*, November 1961, pp. 351-368.

25 Merton J. Peck and F. M. Scherer, *The Weapons Acquisition Process: An Economic Analysis* (Harvard Business School Division of Research, 1962), pp. 254-263 and 276-281. The manuscript was in draft form by the summer of 1961, when Peck joined the Department of Defense staff.

26 Ibid., p. 261.

27 Ibid., pp. 254-263 and 276-281.

assumptions.[28] In a simulation analysis entailing pure parallel path strategies, he found that the maximum surplus of benefits minus R&D costs was gained by supporting more parallel paths, the deeper was the stream of benefits arising from successful projects.

The time-cost tradeoff, however, was highly sensitive to the single-approach *ex ante* probability of success. With success probabilities on the order of 0.2 -- i.e., analogous to success probabilities in the clinical testing of drugs -- from 10 to 20 parallel paths were warranted. With success probabilities of one in one hundred, however - more favorable than what is typically experienced in pre-clinical drug candidate screening - supporting as many as 200 parallel paths was warranted, with sufficiently rich possibilities and deep post-success benefit streams.

A further contribution was made by Abernathy and Rosenbloom, who explicitly modeled the choice between a parallel strategy, defined as “the simultaneous pursuit of two or more distinct approaches to a single task,” and the alternative sequential strategy, which involves selecting

28 F.M. Scherer, "Time-Cost Tradeoffs in Uncertain Empirical Research Projects," *Naval Research Logistics Quarterly*, March and September 1966; reprinted as Ch. 4 in F.M. Scherer, *Innovation and Growth Schumpeterian Perspectives*, MIT Press, 1984, pp. 67-82. Sensitivity to mixtures of parallel and sequential strategies is analyzed in F.M. Scherer, "Parallel Paths Revisited," John F. Kennedy School of Government working paper RWP07-040, September 2007, pp. 1-24.

"the best evident approach, taking up other possibilities only if the first proves unsuccessful."[29] They emphasized that "initial judgments of cost, performance, and value are [generally] highly inaccurate," so that a parallel development strategy serves as an important hedge "against the consequences of failure."[30]

A Dartboard Experiment

To explore how uncertainty about payoff magnitudes affects parallel path strategy choices, we extend here Scherer's earlier and more limited simulation analysis.[31] The selection of R&D projects supported to their final outcomes is modeled as throwing darts at a dartboard, the cells of which are the varying payoffs contingent upon research and marketing success. We assume that the returns from introducing new pharmaceuticals are highly skew and can be represented by a log normal distribution. That is, where N(0,1) is a random variable distributed normally with mean of zero and variance of 1, the distribution of payoffs is given by:

[29] William J. Abernathy and Richard S. Rosenbloom, "Parallel Strategies in Development Projects," *Management Science*, Vol. 18, June 1969, p. 486.
[30] Ibid., pp. 488, 502.
[31] F.M. Scherer, "Schumpeter and the Micro-Foundations of Endogenous Growth," in Horst Hanusch and Andreas Pyka, eds., *The Elgar Companion to Neo-Schumpeterian Economics*, Edward Elgar: 2007, pp. 682-685.

(1) $$D(P) = k X^{N(0,1)}$$

where D(P) is the distribution function, and k and X are scaling parameters; X is arbitrarily set at 10 and k at 1000 (e.g., dollars, multiplied by whatever further scaling parameter is suited to reflect market realities).

To represent the considerable uncertainty associated with the research process, “throws” cannot be directed specifically at the cells with the highest payoffs but instead are randomly distributed, with equal probability, to any of 100 possible cells. R&D costs per "throw" are also permitted to vary, from zero to $12,000. The strategies are purely parallel; no allowance made for strategies in which a smaller number of throws is attempted at the start but then followed by more throws if the objectives are not attained.

Under conditions of certainty, equivalent here to having a perfect aim, the decision-maker would throw a single dart at each cell for which the payoff exceeds the cost of the throw. With the assumed log normal payoff distribution, the average number of such throws varied with R&D cost as follows:

R&D Cost	No. of Throws
$12,000	15
10,000	17
8,000	19
6,000	22
4,000	29
2,000	39
0	100

As expected, when costs are zero, dart-throwing with perfect aim continues until all hundred cells are covered.

In each experiment, additional "hits" on the same payoff cell are considered to add no incremental value. This result reflects the real-world case that when, say, two virtually identical products are launched with the same product characteristics, each product shares the anticipated payoff. In experiments with 100 trials, the average number of duplicated "hits" was on the order of 36, and even with only five trials, occasional double hits were recorded. That some payoff cells are not exploited explains why the optimal number of trials can exceed 100 with low R&D costs per trial: one keeps trying in the hope of hitting untapped payoffs.

A key assumption in the analysis was that each trial's "hit" location was statistically independent of other trials. This assumption could be violated in reality when the targeting of individual trials is positively

correlated, e.g., when a single company launches multiple parallel trials but favors certain broad technical approaches over others. If the number of multiple "hits" is increased for this reason, average net payoffs are lower for any given number of trials.

To achieve reasonably general results in the face of widely varying payoffs, forty full experiments were carried out. For each experiment, a new set of 100 payoffs distributed according to equation (1) was generated, taking care to choose a different normal distribution "seed" for each iteration. As expected, right-hand tail values varied widely across experiments. The largest single extreme payoff value was $1,065,124; the minimax (i.e., the lowest maximum across 40 experiments) was $58,010; the mean among the 40 experiments' maxima was $334,532. At the other extreme, many payoffs were minimal; and the average payoff across all forty experiments was $7,032.[32]

Figure 1 summarizes the results for the forty complete experiments, with the number of trials per experiment ranging from 5 to 100. The values graphed are total payoffs for a given number of trials, averaged across all 40 experiments, less total R&D costs, measured by the

32 For those who doubt that random sampling from skew distributions can generate such widely varying results, see the whole-pharmaceutical industry simulation in Scherer and Harhoff, supra note 11, pp. 562-564; and William Nordhaus, "Comment," *Brookings Paper on Economic Activity: Microeconomics* (1989), pp. 320-325.

assumed cost per trial times the number of trials. Consistent with expectations, the net value-maximizing number of "throws" was higher, the lower the R&D cost per "throw," with optima ranging from 25 "throws" to more than 100 "throws" at zero R&D costs.

At low R&D costs -- $4,000 per trial or less -- average net payoffs are also maximized by extending the number of trials to more than 100, which means attempting (given duplicates, unsuccessfully) to hit every cell on the dartboard. With R&D costs of $6,000, two local maxima emerged -- one with 20 trials and an average net payoff of $120,650, and a maximum maximorum at 50 trials with an average net payoff of $149,829 after deducting the $300,000 total R&D cost per experiment.[33] With still higher R&D costs, the 20-trial strategy dominates, so that at R&D costs of $8,000 per trial, there are mean net payoffs of $80,650 with 20 trials as compared to $62,979 with 40 trials.

Given the substantial variability of payoffs stemming from the log normal distribution, whose use we justify below, what we conclude from this experiment is as follows: **when R&D payoffs per trial approach R&D costs, leading to**

[33] This duality results from the considerable variability of outcomes even with 40 experiments. The 20-throw experiments were apparently unusually lucky. Asymptotically, a single optimum would emerge.

break-even returns, the strategy that maximizes the expected value of net payoffs lies somewhere between 15 and 40 trials.

To be sure, the optimal number of parallel paths hinges on our assumption that the payoff matrix contains one hundred payoff possibilities. In reality, the number of opportunities even at the clinical development stage could be larger or smaller. Therefore, this analysis only demonstrates that parallel paths are desirable under certain circumstances. It cannot show, without appropriate adaptation, how many parallel paths are optimal in a specific real-world situation. However, the optimal number will expand with the number of possible technological opportunities.

The Structure of Pharmaceutical Research and Development

We turn now to features of pharmaceutical research and development that relate to the parameters assumed in the simulation analysis. Of particular relevance is the striking shift that has occurred in the degree of vertical integration. Since the biotechnology revolution in pharmaceutical research,[34] an increasing fraction of

[34] Alexander Scriabine, "The Role of Biotechnology in Drug Development," in Ralph Landau et al. eds., *Pharmaceutical Innovation*, Chemical Heritage Press, 1999, pp. 271-297.

exploratory (molecule discovery) research has been carried out in small, often single-product, firms. Frequently, these smaller research entities are start-up biotech firms. In contrast, the major pharmaceutical companies have retained their long-standing dominance in preparing New Drug Applications (NDA) for the FDA along with the detailed and highly expensive clinical testing required for new drugs.[35]

This pattern is apparent in Scherer's study of the origins of 85 new medical entities approved by the Food and Drug Administration between 2001 and 2005. Examining the patents associated with NDAs submitted for regulatory approval, he finds that 47 percent were issued to firms or non-profit entities with names different from those of the ultimate FDA approval recipient. An even higher 54 percent of the earliest patents originated from outsiders. Although some of these cases may have involved subtle cross-ownership ties, he concludes that the leading pharmaceutical companies have come to rely heavily on outsiders for the pharmaceutical innovations they eventually bring to market.[36]

[35] William S. Comanor, "The Economics of Research and Development in the Pharmaceutical Industry," in Frank A. Sloan and C.R. Hsieh, *Pharmaceutical Innovation*, Cambridge University Press, 2007, pp. 54-72.
[36] F.M. Scherer, 2010, p. 552.

In their interactions with these smaller research-oriented firms, Big Pharma companies fill an essential economic role. Biotech firms typically enjoy the advantages of a rapidly advancing scientific base, Ph.D.-intensive staffs, and a vast trove of unexploited medical possibilities, all in sharp contrast to the apparently growing obsolescence of the small-molecule discovery techniques on which Big Pharma companies have traditionally focused. On the other hand, the large companies commonly have the resources and expertise needed to support large-scale clinical trials. They also have the ability to shepherd the results through the labyrinthine Food and Drug Administration approval process.

These complementarities offer strong incentives for collaboration. Some are organized through outright mergers, although there can be difficulties in assimilating the loosely-structured, basic science-oriented researchers of biotech companies into the more bureaucratic and applications-oriented laboratories of traditional large pharmaceutical companies. Many of these collaborations take the form of alliances, under which the major companies provide financial support for on-going research efforts in return for some form of licensing arrangement on any new drugs resulting from the process.

The decisions of the major pharmaceutical companies on which biotech advances to support can have a major effect on whether particular new drugs are introduced. To be sure, there are circumstances where a large company will support more than a single independent biotech research program in the hope that one is successful.[37] However, even though numerous research efforts may be carried on within smaller companies at any moment in time, only a relatively few receive the follow-on industry funding and support needed for large-scale testing and commercialization. For this reason, as the number of companies available to assist and support biotech companies R&D efforts declines, so will the number of independent paths that are likely to be supported.

At the same time, the large drug companies have continued to pursue some discovery activities in their own laboratories, sometimes even concurrently with externally supported efforts. In path-breaking research, Cockburn and Henderson provide detailed descriptions of the internal discovery activities pursued in ten large companies during the 1980s.[38] They report that large companies pursue on

[37] Iain Cockburn, Personal communication of February 15, 2011 and email message of March 25, 2011.
[38] Iain Cockburn and Rebecca Henderson, "Racing to Invest? The Dynamics of Competition in Ethical Drug Discovery," *Journal of Economics and Management Strategy*, Vol. 3, Fall 1994, pp. 481-519; "Scale, Scope, and Spillovers: the Determinants of Research Productivity in Drug Discovery," *RAND Journal of Economics*, Vol. 27, Spring 1996, pp. 32-59; "Scale and Scope in Drug Development:

average about ten substantial discovery programs per year, directed towards particular medical or therapeutic objectives that might span the entire range of biopharmaceutical research.[39] Such programs cost on average about $600,000 annually in 1986 dollars. In addition, the respondent companies also tended to support about six smaller programs, which could cost about $10,000 per year.[40]

In the Discovery phase of pharmaceutical R&D, the critical factor for innovation is the number of molecules carried forward into succeeding stages of the R&D process. Although much of this scientific work is carried out within smaller biotech companies, the decisions of the larger companies as to which research projects to provide financing and support can largely determine their outcomes.

The Discovery phase of the R&D process comprises a minority share of R&D dollars spent by Big Pharma companies. According to Cockburn and Henderson, about two-thirds of R&D dollars are used for drug Development rather than drug Discovery,[41] where Development entails the translation of new molecules into marketable products.

Unpacking the Advantages of Size in Pharmaceutical Research," *Journal of Health Economics*, 2001, pp. 1-25.

[39] Discovery programs are defined by three conditions: a separate budget unit, a designated collection of people engaged in the research work, and a specified objective. Although different companies may use different terminology, all three conditions must be met for the designation of a research program. These programs may include more than one target molecule and are generally disease-specific efforts. Cockburn, 2011.

[40] Cockburn and Henderson, 1996, p. 43.

[41] Cockburn and Henderson, 2001, p. 5.

Costs are greater there because marketability requires regulatory approval, which demands up to four phases of very costly testing procedures. In 1990, the average Development program[42] lasted just under five years and cost about $200 million.[43] Cockburn and Henderson find that Development projects can be quite risky, with

> on average, only one in five of the compounds that begun substantial clinical testing in our data resulting in the filing of an application for new drug approval (NDA), and even fewer were granted an NDA and reached the marketplace.[44]

On a per-firm basis, the average firm in their sample of ten companies had underway just under sixteen Development programs each year. Therefore, the typical drug company in the sample originated between three and four new programs per year.[45] Moreover, the average firm had programs in more than fourteen therapeutic areas per year.[46] Dividing their 16 programs by 14 therapeutic areas, we conclude that the large companies have tended to limit their development activities to a single program within any given therapeutic area.

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[42] Development programs are typically molecule-specific, or limited to a closely related set of molecules. Cockburn, 2011.
[43] Cockburn and Henderson, 2001, p. 4.
[44] Ibid.
[45] Development programs last about 5 years and the average firm is engaged in 16 of them; then dividing 16 by 5 suggests the average number that need be started each year to maintain this level of activity.
[46] Cockburn and Henderson, 2001, pp. 8-9.

To validate this observation, we examined the disease areas subject to Phase III clinical trials for the five largest U.S. companies for the years 2009 through 2010. Our findings are as follows:

Merck engaged in 25 trials, of which 2 were for the same condition; thus 92 percent were not duplicated.
Johnson & Johnson engaged in 21 trials, of which 2 were for the same condition; thus 90 percent were not duplicated.
Pfizer engaged in 12 trials, of which 2 were for the same condition; thus 83 percent were not duplicated.
Lilly engaged in 13 trials, of which 7 were for the same condition; thus 46 percent were not duplicated.
Bristol-Myers Squibb engaged in 8 trials, of which 2 were for the same condition; thus 75 percent were not duplicated.[47]

These five companies together engaged in 79 trials, of which 15 represented parallel efforts; thus 81 percent were not duplicated in terms of their therapeutic goals. While these statistics suggest some degree of parallelism at the Development stage, it is relatively modest.

These findings have direct bearing on our earlier analysis of parallel research paths. Although the larger companies sometimes adopt a parallel path strategy at the Discovery stage by supporting one or more external programs along with an internal one, that rarely occurs at the Development stage. In particular, these data indicate that

[47] These findings are compilations from the data available on the www.clinicaltrials.gov web site.

large companies, with the apparent exception of Lilly,[48] rarely pursue more than a single program in any given therapeutic area.

One explanation is that introducing a second product in the same therapeutic area is not likely to increase a company's sales proportionately. Except in rare, breakthrough cases, patented products within a therapeutic area compete with each other,[49] and therefore will generally draw a proportion of their sales from the company's other products. The incentive to bear the high costs of Development programs is therefore attenuated as compared with research efforts carried out in separate firms.[50]

From this brief discussion of pharmaceutical R&D activities, we can infer the following conclusion: **the number of paths pursued at the Development stage of pharmaceutical R&D in individual therapeutic areas is not likely to exceed by much the number of large pharmaceutical companies.**

Even when development projects succeed and lead to new product introductions, considerable uncertainty remains

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[48] On Lilly's deviant strategy, see Bernard Munos, "Lessons from 60 Years of Pharmaceutical Innovation," *Nature Reviews/ Drug Discovery*, Vol. 8, December 2009.

[49] Z. John Lu and William S. Comanor, "Strategic Pricing of New Pharmaceuticals," *Review of Economics and Statistics*, Vol. 80, Feb. 1998, pp. 114-115.

[50] This argument is hardly new as a variation of it appeared sixty years ago. See William J. Fellner, "The Influence of Market Structure on Technological Progress," *Quarterly Journal of Economics*, Vol. 65, November 1951, pp. 556-577. See also F.M. Scherer and David Ross, *Industrial Market Structure and Economic Performance*, 3rd ed., 1990, Ch. 17, pp.

about the returns that follow. In a series of papers applicable to the 1970s, 1980s and 1990s, Grabowski and colleagues have investigated the distribution of net economic returns from new drugs.[51] Most recently, they report net product quasi-rents before deduction of R&D costs for the 118 new chemical entities introduced between 1990 and 1994, ordered by deciles from highest to lowest. The distribution is highly skew, with the top decile alone accounting for 52 percent of the aggregate present values across all 118 new drugs.[52] This degree of skewness, moreover, is not exceptional. They also find that "the top decile has accounted for between 46 and 54 percent of the overall returns over the four sample cohorts … analyzed."[53]

This evidence supports our use of the log normal distribution to describe the payoffs from innovation, even though that distribution is more skew than the distribution of quasi-rents reported by Grabowski and colleagues. The top ten percent cohort in the log normal distribution indicated in equation 1 captures roughly 80 percent of total payoffs. However, Grabowski and colleagues analyze

[51] Henry Grabowski, John Vernon and Joseph A. DiMasi, "Returns on Research and Development for 1990s New Drug Introductions," *Pharmacoeconomics*, Vol. 20, 2002, pp. 11-29; Henry G. Grabowski and John M. Vernon, "Returns to R&D on New Drug Introductions in the 1980s," *Journal of Health Economics*, Vol. 13, 1994, pp. 383-406; and "A New Look at the Returns and Risks to Pharmaceutical R&D," *Management Science*, Vol. 36, July 1990, pp. 804-821.

[52] Grabowski, Vernon and DiMasi, 2002, p. 22.

[53] Ibid., p. 23. The four cohorts examined are 1970-74, 1975-79, 1980-84 and 1990-94.

the returns from new molecules *approved* by the Food and Drug Administration and presumably marketed after passing that hurdle. Our analysis deals instead with the development and testing activities that *precede* FDA approval. As noted above, among the molecules carried into clinical testing in the United States, fewer than one in five are eventually approved. If the number of molecules that begin rather then complete clinical trials is the sample base, the top ten percent of NDA recipients is roughly equivalent to the top 2.5 percent of the sample entering clinical testing. The top 2.5 percent in our log normal sample account for about 54 percent of total sample payoffs – quite similar to the range reported by Grabowski and Vernon.[54] **The log normal distribution employed above therefore tracks the empirical evidence well.**

Rent-seeking and Social and Private Rates of Return

Under a rent-seeking model of R&D investment, rivals compete by making R&D "bets" that continue so long as expected rewards exceed expected costs.[55] Equilibrium is

[54] If the sample is extended to the much larger number of molecules not carried into human testing, the share of the NDA recipients analyzed by Grabowski et al. falls even more. Molecules not receiving marketing approval might nevertheless have some value in terms of their information spillover value. The median payoff in our full experiment sample was $950 – i.e., in the low range of plausible spillover values.

[55] For an early description of this process, see William S. Comanor, "Research and Competitive Product Differentiation in the Pharmaceutical Industry in the United States," *Economica*, Vol. XXXI, November 1964, pp. 372-384.

reached when expected rewards approximate expected costs. Compelling evidence suggests that such rent-seeking behavior prevails in regard to pharmaceutical R&D.

Grabowski and colleagues studied the relationship of average discounted quasi-rent values to R&D costs for various periods from 1970 through the 1990s.[56] They found that new product revenues from the 1990s only slightly exceeded R&D costs; specifically, that "the IRR (internal rate of return) is 11.5% and can be compared with our cost-of-capital estimate of 11%. Hence, the industry mean performance is positive but only by a small amount."[57]

This finding is similar to that reached in a government study that surveyed new chemical entities introduced between 1981 and 1983. Its conclusion was that

> the average revenue per compound was $36 million more in NPV (net present value) than was needed to bring forth the research on the drugs introduced. … This excess would be eliminated if annual revenues per compound were reduced by 4.3 percent.[58]

The study found that large drug companies earned rates of return on their investment only two or three percentage points higher than the real cost of their financial capital.[59]

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[56] Supra note 51.
[57] Garbowski, Vernon, and DiMasi, op. cit., 2002, p. 20.
[58] U.S. Congress, Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks and Rewards*, OTA –H-522, Washington, DC: US Government Printing Office, February 1993, p. 94.
[59] Ibid. See also Scherer, 2010, p. 562.

Both studies conclude that net revenues from pharmaceutical R&D exceeded the associated research costs, including those of failures, by only small amounts. **They support the inference that a zero net expected profit rent-seeking process was approximated.** Recall the simulation analysis presented above. Along the zero net payoff line in Figure 1, we identify the number of "dart throws" or research projects required to reach a zero net return equilibrium. In effect, those values describe the numbers of research paths needed to reach a competitive balance between expected payoffs and costs.

Furthermore, this evidence reflects the private returns from pharmaceutical R&D rather than those that accrue more broadly to society: there can be wide differences between private and social returns. If social benefits, including consumer surpluses and the value of non-market externalities, exceed their associated private benefits, then fewer parallel paths might be pursued by private firms than would be socially optimal. On the other hand, since rivals confront the same set of opportunities,[60] parallel efforts are likely to occur. Whether the parallelism thus engendered is sufficient to meet the

[60] As suggested by Cockburn and Henderson, 1994, pharmaceutical R&D decisions are driven primarily by technological opportunities along with the firm's specific human capital capabilities. See also Scherer, 2010, p. 568.

requirements for a social optimum is unknown. What is clear, however, is that reducing the number of rival firms tends to limit the extent of parallelism in R&D. Therefore, if parallelism had reached near optimal levels under rent-seeking behavior before consolidation, then reducing the number of rivals leads to fewer parallel paths and a slower rate of pharmaceutical innovation.

There is support for this conclusion from a study that correlated the number of new molecular entities (NME) approved by the FDA with the number of innovating companies. The author reports that these factors are "closely correlated in a nonlinear relationship that explains 95% of the changes in expected NME output by changes in the number of companies."[61] He observes further that the larger pharmaceutical companies "have delivered innovations at a constant rate for almost 60 years."[62] In that case, reducing the number of innovating companies implies fewer innovations, which is a conclusion consistent with the analysis above of parallel research paths.

As indicated above, a critical factor is the extent of the gap between social and private benefits from pharmaceutical research. In pioneering research, Mansfield

[61] Munos, op. cit,. p. 963.
[62] Ibid., p. 961.

and colleagues report that innovators' median profits from their research efforts were 25 percent before tax, while the median social return was on the order of 56 percent, or roughly twice the private return.[63]

In a more recent study limited to pharmaceutical R&D, Lichtenberg studied the impact of new drug approvals on reduced mortality. Using a benchmark estimate of $25,000 per life-year saved, he estimated the social rate of return from pharmaceutical innovation at approximately 68 percent per annum.[64] This value is nearly six times Grabowski's figure for the private returns from pharmaceutical research and development.

Lichtenberg acknowledges two sets of extenuating factors. The first is that if life-years are valued instead at $10,000, his estimated return falls to 27 percent. His second factor, however, cuts in the opposite direction. It rests on the fact that new drugs convey many social benefits beyond reduced mortality, such as reduced sickness and morbidity, fewer workdays and schooldays lost,

63 Edwin Mansfield et al., "Social and Private Rates of Return from Industrial Innovations," *Quarterly Journal of Economics*, vol. 91, May 1977, pp. 221-240. See more generally Bronwyn Hall, Jacques Mairesse, and Pierre Mohnen, "Measuring the Returns to R&D," in Bronwyn Hall and Nathan Rosenberg, eds., *Handbook of the Economics of Innovation* (North-Holland: 2010), vol. II, pp. 1033-1082.

64 Frank R. Lichtenberg, "Pharmaceutical Innovation, Mortality Reduction, and Economic Growth," in Kevin M. Murphy and Robert H. Topel, eds., *Measuring the Gains from Medical Research, an Economic Approach*, 2003, University of Chicago Press, p. 102.

and a generally improved quality of life.[65] Given the constraining assumption of his empirical analysis, Lichtenberg concludes that the social returns from new drug development should be even higher than the 68 percent return obtained from his statistical analysis.

These findings have direct implications for the optimal number of parallel research paths. Where the social returns from R&D outlays greatly exceed their corresponding private returns, the desired number of parallel paths is larger than it would be otherwise. If parallel paths are mainly induced through rent-seeking behavior that carries R&D to the point where private returns approximately equal costs, then a decline in the number of rival firms could lead to fewer parallel approaches and increase the likelihood that the number of research paths pursued is socially sub-optimal. As a result, **recent mergers that necessarily led to fewer parallel efforts lowered the rate of pharmaceutical innovation.**

Policy Conclusions

From their consideration of the Pfizer-Wyeth merger,

[65] Ibid. See also Frank R. Lichtenberg, "Pharmaceutical Knowledge -- Capital Accumulation and Longevity," in C. Corrado, J. Haltiwanger, and D. Sichel, eds., *Measuring Capital in the New Economy*, University of Chicago Press: 2004; and "The Benefits and Costs of Newer Drugs: Evidence from the 1996 Medical Expenditure Panel Survey," National Bureau of Economic Research Working Paper No. 8147, 2001.

the Federal Trade Commission found that the merger was "unlikely to have an adverse impact on the development of human pharmaceutical products."[66] That conclusion runs counter to that reported in a statistical study of pharmaceutical mergers:

> Another surprising finding is that companies that do essentially the same thing can have rates of NME output that differ widely. This suggests there are substantial differences in the ability of different companies to foster innovation. In this respect, the fact that the companies that have relied on M&A (Mergers and Acquisitions) tend to lag behind those that have not suggests that M&A are not an effective way to promote an innovation culture or remedy a deficit of innovation.[67]

The analysis offered here also conflicts with the FTC position. So important is the development of new pharmaceuticals for society's welfare, and so problematic is the on-going decline in new drug development, that the U.S. government is considering the establishment of a new federal research center to pursue drug development.[68] There is an important public interest in promoting rapid pharmaceutical innovation, and policies that foster large numbers of parallel paths directed towards the development of effective new drugs can be an important step towards that objective.

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[66] Federal Trade Commission, Letter to Drs. Comanor and Scherer, January 25, 2010.
[67] Munos, op. cit., p. 961.
[68] Gardiner Harris, "A New Federal Research Center Will Help to Develop Medicines,' *The New York Times*, January 23, 2011, pp. A1-21.

To be sure, the pursuit of parallel research paths is not limited to major pharmaceutical companies. However, as the Cockburn–Henderson data show, the larger companies engage on average in Development programs that are typically limited to a single entrant in a therapeutic area. Although smaller biotech firms add to the extent of parallelism in Discovery programs, that is not so for Development programs which typically require the financial and technical support available only in the larger companies. The Big Pharma companies play a critical role, particularly in the clinical testing process.

Although one cannot know definitely whether the pharmaceutical industry, or individual member firms, were investing socially optimal amounts in research and development when industry concentration was lower, we can observe the effects of the recent large mergers. Even prior to these mergers, the amounts allocated to R&D by both Pfizer and Merck led to what was generally considered, both internally and by outside expert opinion, a disappointing yield of new pharmaceutical agents.

The consequences of the two recent large mergers have been distinctly negative. Before their merger, Pfizer and Wyeth together were investing approximately $11.3 billion in R&D annually, while afterwards they spent $9.4 billion in

2010 and have announced plans to reduce spending still further to between $6.5 and $7 billion by 2012.[69] This is a decline of 57 to 62 percent from prior levels. At a minimum, one major Pfizer R&D laboratory will be closed and another substantially downsized.[70] Similarly, Merck announced that it would close at least three R&D facilities but with the total R&D spending reduction left unspecified.[71] The effects of these mergers on R&D spending and employment were clearly negative, leading directly to a reduction in the degree of parallelism in drug development.

Permitting horizontal mergers between large pharmaceutical companies appears to have limited the desirable pursuit of independent parallel paths in pharmaceutical development. We can also infer that it contributed to the observed decline in the rate of pharmaceutical innovation.

[69] Elkind and Reingold, *Fortune*, August 15, 2011.
[70] Ibid.
[71] "FierceBiotech.com," April 28, 2010.