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Mergers and Innovation in the Pharmaceutical Market

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Mergers and Innovation in the Pharmaceutical Market
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MERGERS AND INNOVATION

IN THE PHARMACEUTICAL INDUSTRY

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<u>Introduction</u>

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 shipments of pharmaceutical products. By 2002,

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[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 add prominence to this question:

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 roughly 22

percent of world-wide spending.[7] In addtion, 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 up to 39

percent of total world-wide spending.

Under existing U.S. antitrust policies, mergers can be

evaluated in terms of their prospective effects on

innovation as well as price levels. We therefore discuss

current policy standards on the importance of innovation to

the antitrust consideration of mergers. Then we shift our

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[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

attention to the theory of parallel research paths and
review relevant prior studies. 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.

Mergers and Innovation

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 case, but then accepted a consent order

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

under which some assets were divested. There was no
mention in any public Commission document of the firms' R&D
activities even though they comprise a main mode of
competition among large pharmaceutical companies.

The antitrust agencies typically focus on prospective
pricing behavior in merger cases. However, considering
innovative behavior is not unprecedented. In the
investigation of a proposed merger between aerospace giants
Lockheed-Martin and Northrop-Grumman during the late 1990s,
for example, the fear that the sources of innovative weapon
systems concepts would be significantly limited was central
to an investigation by the Department of Justice. No
complaint was brought, however, because Lockheed realized
that there was opposition to its merger in both the
antitrust agencies and the Department of Defense, and
voluntarily abandoned it.

On August 10, 2010, the Department of Justice and FTC
issued revised *Horizontal Merger Guidelines,* which were
said in the overview to "describe the principal analytical
techniques and the main types of evidence on which the
Agencies usually rely to predict whether a merger may
substantially lessen competition."   Section 6.4 of those
Guidelines addresses "Innovation and Product Variety." It
states in part:

> Competition often spurs firms to innovate. The
> Agencies may consider whether a merger is likely to
> diminish innovation competition by encouraging the
> merged firm to curtail its innovative efforts below
> the level that would prevail in the absence of the
> merger. That curtailment of innovation could take the
> form of reduced incentive to continue with an existing
> product-development effort or reduced incentive to
> initiate development of new products....

Although the new Guidelines were not yet published at the time of the Merck - Schering-Plough and Pfizer-Wyeth merger proposals, they were believed to reflect U.S. antitrust agency practice, must at least have been under discussion at the time of the giant pharmaceutical mergers, and were anticipated at least in the Lockheed - Northrop deliberations.[9] Nevertheless, the Federal Trade Commission chose not to act. We believe its inaction was mistaken.

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

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[9] Earlier, in 1995, the agencies released *Guidelines for the Licensing of Intellectual Property* that among other things proposed the concept of "innovation markets." The proposal was controversial and led to various dissenting articles. See 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; Richard T. Rapp, "The Misapplication of the Innovation Market Approach to Merger Analysis," *Antitrust Law Journal,* Vol. 64, Fall 1995; 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; and 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.

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

upon technical success.[10]   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, 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.[11] 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.

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.[12] Introducing the prize proposal to Parliament,

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10   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.

[11] 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.

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

Isaac Newton offered a non-exclusive list of specific

technical avenues. The one he considered least promising *ex

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.[13]

Recognizing the advantages of packing transistors into

much smaller cubic volumes, the U.S. military services

issued a dozen parallel R&D contracts to induce a

solution.[14] 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.[15]

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

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13 See James Phinny Baxter, *Scientists Against Time,* (MIT Press, 1986), pp. 433-436.
14. See F. M. Scherer, *Industry Structure, Strategy, and Public Policy* (New York: HarperCollins, 1996), pp. 204-204.
15. 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.

specific numerical example for fighter aircraft development
that parallel development strategies could yield more
advantageous results than a monolithic approach.[16]

Soon thereafter, M.J. Peck and F.M. Scherer identified
parallel R&D paths as one element of a broader time-cost
tradeoff problem in weapons development.[17] 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.[18]

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.[19] They argue that R&D is an investment seeking to
yield a stream of benefits in the future, pursuing more
sequential approaches to research and development 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

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

17 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.

18 Ibid., p. 261.

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

R&D project scheduling alternatives, finding that a convex time-cost tradeoff set persisted over a broad range of assumptions.[20] 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, assuming the presence of promising alternatives. 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

20 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.

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 "the best evident approach, taking up other possibilities only if the first proves unsuccessful."[21] 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."[22]

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.[23] 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,

[21] William J. Abernathy and Richard S. Rosenbloom, "Parallel Strategies in Development Projects," *Management Science*, Vol. 18, June 1969, p. 486.
[22] Ibid., pp. 488, 502.
[23] 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.

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:

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

where D(P) is the distribution function; k and X are
scaling parameters; and 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 is 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 reflects the real-world case that when, say, two

virtually identical products are launched with the same

product characteristics, the two share 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.[24]

Figure 9 summarizes the results for the 40 complete experiments, with the number of trials per experiment

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24 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 Dietmar Harhoff, supra note 11, pp. 562-564; and William Nordhaus, "Comment," *Brookings Paper on Economic Activity: Microeconomics* (1989), pp. 320-325.

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

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.[25] 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

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[25] 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.

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

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 plausible 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,[26] an increasing fraction of exploratory (molecule discovery) research has been carried out in small, often single-project, 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.[27]

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 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.[28]

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[26] Alexander Scriabine, "The Role of Biotechnology in Drug Development," in Ralph Landau et al. eds., *Pharmaceutical Innovation,* Chemical Heritage Press, 1999, pp. 271-297.
[27] 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.
[28] 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 collaborations. 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 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.[29] 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 and an unknown but not unsubstantial number of promising molecules left unsupported. 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 likely to be supported.

At the same time, the large drug companies have continued to pursue some discovery activities in their own laboratories, sometimes 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.[30] They report that large companies pursue on

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[29] Iain Cockburn, Personal communication of February 15, 2011 and email message of March 25, 2011.
[30] 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;

average about ten substantial discovery programs per year,
directed towards particular medical or therapeutic
objectives that might span the entire range of
biopharmaceutical research.[31]   Such programs cost on average
about $600,000 annually in 1986 dollars.   In addition, the
respondent companies also tended to support on average six
smaller programs, which could cost roughly $10,000 per
year.[32]

In the discovery phase of pharmaceutical R&D, the
critical factor for innovation is the number of molecules
carried forward into succeeding stages.   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 consumes 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

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

[31] 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.

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

than drug discovery,[33] where development entails the translation of promising new molecules into marketable products. 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[34] lasted just under five years and cost about $200 million.[35] 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.[36]

On a per-firm basis, the average firm in their sample of ten companies had underway nearly sixteen development programs per year. Therefore, the typical drug company in the sample must have originated between three and four new programs per year.[37] Moreover, the average firm had programs in more than fourteen therapeutic areas.[38] Dividing their 16 programs by 14 therapeutic areas, we conclude that the large companies have tended to limit

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[33] Cockburn and Henderson, 2001, p. 5.
[34] Development programs are typically molecule-specific, or limited to a closely related set of molecules. Cockburn, 2011.
[35] Cockburn and Henderson, 2001, p. 4.
[36] Ibid.
[37] 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.
[38] Cockburn and Henderson, 2001, pp. 8-9.

their development activities to a single program within any given therapeutic area.

To test this finding, we examined the disease areas subject to Phase III clinical trials for the five largest U.S. companies for the years 2009 and 2010. Our results are as follows:

<u>Merck</u> engaged in 25 trials, of which 2 were for the same condition; thus 92 percent were not duplicated.

<u>Johnson & Johnson</u> engaged in 21 trials, of which 2 were for the same condition; thus 90 percent were not duplicated.

<u>Pfizer</u> engaged in 12 trials, of which 2 were for the same condition; thus 83 percent were not duplicated.

<u>Lilly</u> engaged in 13 trials, of which 7 were for the same condition; thus 46 percent were not duplicated.

<u>Bristol-Myers Squibb</u> engaged in 8 trials, of which 2 were for the same condition; thus 75 percent were not duplicated.[39]

The 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 this suggests some degree of parallelism at the development stage, it is relatively modest.

These findings can be interpreted in light of our earlier analysis of parallel research paths. Although the larger companies sometimes adopt a parallel path strategy

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

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, the data indicate that large companies, with the apparent exception of Lilly,[40] 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,[41] and therefore will draw a proportion of their sales from the firm'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.[42]

From this brief discussion of pharmaceutical R&D activities, we 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.**

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

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

[42]   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.

Even when development projects succeed and lead to new product introductions, considerable uncertainty remains 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.[43] 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.[44] 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."[45]

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 of

[43] 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.
[44] Grabowski, Vernon and DiMasi, 2002, p. 22.
[45] Ibid., p. 23. The four cohorts examined are 1970-74, 1975-79, 1980-84 and 1990-94.

equation (1) captures roughly 80 percent of total payoffs. However, Grabowski and colleagues analyze 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.[46] 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

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[46] 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.

expected rewards exceed expected costs.[47] Competitive

equilibrium is reached when expected rewards approximate

expected costs. Compelling evidence suggests that such

rent-seeking behavior prevails in regard to pharmaceutical

R&D.

Henry Grabowski and colleagues studied the

relationship of average discounted quasi-rent values to R&D

costs for various periods from 1970 through the 1990s.[48]

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."[49]

A similar conclusion was 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.[50]

The study found that large drug companies earned rates of

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[47] 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.

[48] Supra note 51.

[49] Garbowski, Vernon, and DiMasi, op. cit., 2002, p. 20.

[50] 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.

return on their investment only two or three percentage points higher than the real cost of their financial capital.[51]

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 earlier. 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. Those values describe the numbers of research paths needed to reach a competitive equilibrium that is based on expected payoffs and costs.

These inferences, moreover, reflect 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

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[51] Ibid. See also Scherer, 2010, p. 562.

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hand, since rivals confront the same set of opportunities,[52] parallel efforts are likely to occur. Whether the parallelism thus engendered is sufficient to meet the 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. 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 variables are "closely correlated in a nonlinear relationship that explains 95% of the changes in expected NME output by changes in the number of companies."[53] He observes further that the larger pharmaceutical companies "have delivered innovations at a constant rate for almost 60 years."[54] In that case, reducing the number of innovating companies

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[52] 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.

[53] Munos, op. cit,. p. 963.

[54] Ibid., p. 961.

implies fewer innovations, which is consistent with the

analysis above of parallel research paths.

Again, a critical factor is the extent of the gap

between social and private benefits from pharmaceutical

research. In pioneering research, Edwin Mansfield and

colleagues reported 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.[55]

In a more recent study limited to pharmaceutical R&D,

Frank 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.[56] This value is nearly six times

Grabowski's figure for the private returns from

pharmaceutical research and development.

Lichtenberg acknowledges two sets of extenuating

circumstances. The first is that if life-years are valued

instead at $10,000, his estimated return falls to 27

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55 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.

[56] 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.

percent. His second caveat, 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, and a generally improved quality of life.[57] Given the constraining assumptions of his empirical analysis, Lichtenberg concludes that the social returns from new drug development are probably even higher than the 68 percent return obtained in 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 by a strictly private calculus. 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 led to fewer parallel efforts reduced the rate of pharmaceutical innovation.**

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[57] 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.

Policy Conclusions

In its consideration of the Pfizer-Wyeth merger, the Federal Trade Commission found that the merger was "unlikely to have an adverse impact on the development of human pharmaceutical products."[58] That conclusion runs counter to one 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.[59]

The analysis offered here also differs from 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.[60] There is an important public interest in promoting rapid pharmaceutical innovation, and policies that foster large

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[58] Federal Trade Commission, Letter to Drs. Comanor and Scherer, January 25, 2010.

[59] Munos, op. cit., p. 961.

[60] Gardiner Harris, "A New Federal Research Center Will Help to Develop Medicines,' *The New York Times*, January 23, 2011, pp. A1-21.

numbers of parallel paths directed towards the development of effective new drugs can be an important step towards that objective.

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 therapeutic area. Although smaller biotech firms add 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. 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 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 post-merger they spent $9.4 billion in
2010 and announced plans to reduce spending still further to
between $6.5 and $7 billion by 2012.[61] This implies 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.[62] Similarly, Merck announced that
it would close at least three R&D facilities, but with the
total R&D spending reduction left unspecified.[63] The effects
of these mergers on R&D spending and employment were clearly
negative, implying 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. And it likely contributed to
the decline in the rate of pharmaceutical innovation.

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[61] Elkind and Reingold, *Fortune,* August 15, 2011.
[62] Ibid.
[63] "FierceBiotech.com," April 28, 2010.

Figure 9

Average Net Payoffs from 40 Dartboard Replications