Mergers and Innovation in the Pharmaceutical Market

William S. Comanor
University of California

F.M. Scherer
Harvard Kennedy School

2011
We appreciate helpful comments and suggestions from Iain Cockburn, H.E. Frech and Rudolph Peritz. We also appreciate the careful research assistance of Karleen Giannitrapani.
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 shipments of pharmaceutical products. By 2002,

---

² Pharmaceutical Research and Manufacturers of America, PhRMA Membership Survey, 2009.
their share had risen to more than 53 percent.\textsuperscript{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.\textsuperscript{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\textsuperscript{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?

\textsuperscript{5} Ibid.
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. In addition, 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

---

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

---

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. 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

---

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{12} Introducing the prize proposal to Parliament,

\footnotesize
\begin{itemize}
\item \textsuperscript{10} Attention to this important distinction was first drawn by Edwin Mansfield and others in \textit{The Production and Application of New Industrial Technology}, Norton: 1977, pp. 22-32.
\item \textsuperscript{12} See Dava Sobel, \textit{Longitude} (New York: Walker, 1995), especially pp. 51-60.
\end{itemize}
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

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.

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.\footnote{Merton J. Peck and F. M. Scherer, \textit{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.} The essence of this strategy was

\begin{quote}
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.\footnote{Ibid., p. 261.}
\end{quote}

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.\footnote{Ibid., pp. 254-263 and 276-281.} 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
R&D project scheduling alternatives, finding that a convex
time-cost tradeoff set persisted over a broad range of
assumptions. 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

---

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
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.” 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.”

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. 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,

---

22 Ibid., pp. 488, 502.
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:

\[
D(P) = k \cdot X^{N(0,1)}
\]

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:

<table>
<thead>
<tr>
<th>R&amp;D Cost</th>
<th>No. of Throws</th>
</tr>
</thead>
<tbody>
<tr>
<td>$12,000</td>
<td>15</td>
</tr>
<tr>
<td>10,000</td>
<td>17</td>
</tr>
<tr>
<td>8,000</td>
<td>19</td>
</tr>
<tr>
<td>6,000</td>
<td>22</td>
</tr>
<tr>
<td>4,000</td>
<td>29</td>
</tr>
<tr>
<td>2,000</td>
<td>39</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

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

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. 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

---

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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{28}


\textsuperscript{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.\textsuperscript{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.\textsuperscript{30} They report that large companies pursue on

\textsuperscript{29} Iain Cockburn, Personal communication of February 15, 2011 and email message of March 25, 2011.
average about ten substantial discovery programs per year, directed towards particular medical or therapeutic objectives that might span the entire range of biopharmaceutical research. 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.

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


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, 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 lasted just under five years and cost about $200 million. 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.

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. Moreover, the average firm had programs in more than fourteen therapeutic areas. Dividing their 16 programs by 14 therapeutic areas, we conclude that the large companies have tended to limit

---

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.
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:

**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.\(^39\)

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

\(^{39}\) 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, 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, 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.

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.

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. 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. 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.”

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

---


44 Grabowski, Vernon and DiMasi, 2002, p. 22.

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. 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

---

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. 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. 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.”

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.

The study found that large drug companies earned rates of

48 Supra note 51.
return on their investment only two or three percentage points higher than the real cost of their financial capital.\textsuperscript{51}

Both studies conclude that net revenues from pharmaceutical R&D exceeded the associated research costs, including those of failures, by only small amounts. \textbf{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

\textsuperscript{51} Ibid. See also Scherer, 2010, p. 562.
hand, since rivals confront the same set of opportunities, 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.” He observes further that the larger pharmaceutical companies “have delivered innovations at a constant rate for almost 60 years.” In that case, reducing the number of innovating companies

---

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

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,
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
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.\textsuperscript{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.

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

59 Munos, op. cit., p. 961.
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.\textsuperscript{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.\textsuperscript{62} Similarly, Merck announced that it would close at least three R&D facilities, but with the total R&D spending reduction left unspecified.\textsuperscript{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.

\textsuperscript{61} Elkind and Reingold, \textit{Fortune}, August 15, 2011.
\textsuperscript{62} Ibid.
\textsuperscript{63} “FierceBiotech.com,” April 28, 2010.
Figure 9

Average Net Payoffs from 40 Dartboard Replications

Average Gross Payoff Less R&D Costs ($000)

Number of Trials in Each Experiment

RD = 0
RD = 2000
RD = 4000
RD = 6000
RD = 8000
RD = 10000