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Title: **Mergers and Innovation in the Pharmaceutical Industry**

Authors: **William S. Comanor and F.M. Scherer·**

Abstract:

Conflicting trends confound the pharmaceutical industry. The productivity of pharmaceutical innovation has declined in recent years. At the same time, the cohort of large companies who are the leading engines of pharmaceutical R&D has become increasingly concentrated. The concurrent presence of these trends is not sufficient to determine causation. In response to lagging innovation prospects, some companies have sought refuge in mergers and acquisitions to disguise their dwindling prospects or 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?

Keywords: Pharmaceutical mergers, Innovation

Author Contact: comanor@ucla.edu

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MERGERS AND INNOVATION IN THE PHARMACEUTICAL INDUSTRY

William S. Comanor and F. M. Scherer

The pharmaceutical industry has encountered a period of dramatic structural change. The first manifestation has been a productivity shock, as the number of new molecular entities approved for introduction into the United States market between 1970 and 2010 grew only slightly despite an increase in inflation-adjusted research and development expenditures at a rate of roughly seven percent per year.[1] As a result, the R&D cost of an average new molecule has skyrocketed -- from roughly $40 million at year 2000 price levels in clinical testing costs alone for drugs introduced during the 1980s to $280 million for 1990s drugs, and even more recently.[2] This has occurred despite the emergence of radically new means to discover candidate molecules -- DNA analysis combined with gene splicing -- and the growth of a new biotech industry oriented around those techniques. Third, because of the expiration of key patents without commensurate replacement, legal changes, and insurance mandates, generic fulfillment of prescriptions has risen from 17 percent in 1980 and 30 percent in 1990 to upwards of 70 percent by number in 2009.[3] Post-patent-expiration price competition has become more intense, compelling main-line drug companies either to innovate or fade away. Fourth, and not unrelated to these trends, the traditional pharmaceutical industry has experienced a wave of mergers, causing the disappearance of many companies that once were at or near the industry's innovative vanguard.

While industry leaders explain their mergers as a response to these shocks and a partial solution to the declining productivity problem, this paper advances the reverse hypothesis: that

1 Scherer (2011).

2 Ibid., 554, summarizing evidence compiled by Joseph DiMasi, Henry Grabowski, and others.

3 Generic Pharmaceutical Association, press release of May 7, 2009.

instead of enhancing R&D productivity, the merger wave has jeopardized it.[4] Our central thesis emphasizes the uncertainties inevitably encountered in new drug discovery and development and the role of "parallel paths" -- i.e., the pursuit of multiple approaches to solving any given medical problem -- in coping with those uncertainties.

The Merger Wave

Before starting our analysis, we present evidence on the contours of recent "Big Pharma" merger activity. Our attention was directed to this phenomenon most dramatically by two massive mergers consummated in 2009: the acquisition of Wyeth Laboratories, fifth-ranked on *Fortune* magazine's 2008 list of U.S.-based pharmaceutical firms, by Pfizer, even before the merger the largest U.S. pharmaceutical producer;[5] and the acquisition by Merck, fourth-ranked on *Fortune's* list, of eighth-ranked Schering-Plough. In 2008, Pfizer invested $7.9 billion for pharmaceutical R&D across its world-wide operations while Wyeth spent $3.4 billion, for a total of $11.3 billion. This sum was 22 percent of the worldwide R&D spending by members of the Pharmaceutical Research and Manufacturers of America (PhRMA) (including 14 entities with home bases overseas).[6] In 2008 Merck expended $4.8 billion on R&D and Schering-Plough $3.5 billion, for a combined total of $8.3 billion, or 17 percent of the PhRMA universe total. Thus, the four merged entities together accounted for 39 percent of PhRMA members' 2008 outlays, and hence must be considered a major element in the progress of pharmaceutical technology.

These mergers were only the high point in a broader trend. Table 1 summarizes the

4 For another analysis reaching similar conclusions but employing a different methodology, see Munos (2009).
5 Pfizer lagged Johnson & Johnson on *Fortune's* sales ranking for 2008 (May 4, 2009, p. F-56), but nearly two-thirds of J&J's sales were in non-pharmaceutical lines.
6 R&D expenditures within the United States by PhRMA members in 2007 -- the last year for which comparable U.S. Census data are available -- were nearly 77 percent of pharmaceutical industry expenditures measured in a U.S. National Science Foundation survey.

principal mergers completed in recent years by the world's twelve leading pharmaceutical producers, ranked by worldwide sales in 2010. Altogether, those firms' positions in 2011 were influenced by 19 significant mergers and acquisitions from 1989 to 2011, not including various smaller consolidations.

The eight largest pharmaceutical sellers, including both domestically and foreign-owned companies, accounted for 36 percent of "pharmaceutical preparation" factory sales in the United States in 1987 and 54.2 percent in 2007 -- the latest year for which Census data are available.[7] Five significant mergers since 2007 have undoubtedly increased the degree of concentration, which is understated as a measure of how technological initiative is structured because the U.S. Census Bureau tally includes the (rapidly increasing) sales of generic drug producers, most of whom perform relatively little R&D. For an alternative way of quantifying these structural changes, one can compare *Fortune_500* sales listings for 1998 and 2011. In each year, the domestic *Fortune* listings included 12 pharmaceutical manufacturers. In 1998, the four sales leaders accounted for 56 percent of the 12 listed companies' sales. In 2011, the four leaders' combined sales share had risen to 70.7 percent.

Parallel Paths and the Dispersion of Technological Initiative

When concentration ratios are analyzed by economists, the conventional rationale is that sufficiently high concentration of sales among the four or eight largest companies in well-defined product line segments can lead to cooperative oligopolistic pricing. This was apparently the principal but not sole focus of U.S. antitrust agencies when they evaluated the most recent Pfizer and Merck mergers, among others.[8] Here we take a different approach. Our central argument is

7 U.S. Bureau of the Census, Census of Manufactures, *Concentration Ratios in Manufacturing: 2007* (retrieved from the Census Bureau web site).

8 Consistent with Horizontal Merger Guidelines amended periodically, most recently section 6.4 of the August 2010 version, the U.S. antitrust agencies also analyze whether a merger is "likely to diminish innovation." Divestitures of

that technological innovation is characterized by major uncertainties, so that it is usually unclear ex ante whether a particular initiative will be successful. Some firms will hesitate to invest at all in R&D; while others may support technical approaches that prove worthless in the end. Technological progress is best achieved in a field like pharmaceuticals when there is widespread dispersion of R&D initiatives both across companies and within them through the exploration of multiple technical paths. In the literature of operations research and (less so) economics, the investment strategies embodying this dispersion of initiatives are called "parallel paths" strategies.[9]

Some history provides perspective. The oldest known conscious use of a parallel paths strategy was the famous British Longitude Prize, announced in 1714, for which many individuals competed to devise a means by which naval ships could determine, short of crashing onto shoals, how far east or west they had travelled. Introducing the prize approach to the British Parliament, Isaac Newton identified five specific technical avenues plus variants. One he considered unpromising -- a clock capable of keeping exact time relative to the Greenwich meridian -- eventually won the prize for Joseph Harrison, but only after the prize committee was "besieged" with proposals (Sobel, 1995, pp. 52-55). During World War II, fearing that Germany might be developing an atomic weapon, the United States Manhattan Project supported five alternative methods of separating the needed fissionable material as well as two completely different

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narrowly defined competing lines or patents have sometimes been required before allowing mergers to go forward. For example, in the Pfizer-Wyeth case, some overlapping assets in the animal health area were voluntarily divested. In addition, Merck and Schering Plough were required to divest certain household pet and (human) nausea therapies. For a list of nine pharmaceutical mergers between 1980 and 1998 on which compulsory licensing of narrowly selected potentially blocking patents was required, see Preis (2005), pp. 108-110.

The authors of this paper submitted in February 2009 a memorandum to the Federal Trade Commission on the Pfizer merger, emphasizing the same points as those analyzed in the present paper. There is no evidence that the Commission pursued the kind of broad analysis suggested here.

9 A pioneering contribution was Richard Nelson (1961). The concept was developed qualitatively by Peck and Scherer (1962, Chapter 9) and extended in numerous dimensions by Scherer (1966) and (2007). For still another approach, see Abernathy and Rosenbloom (1969).

approaches to bomb design -- the uranium gun-barrel and a plutonium implosion device.[10] The five separation approaches, if carried through to a full technological demonstration, were expected together to cost $500 million, which at the time was one-third percent of annual U.S. GDP. A decade earlier, du Pont synthesized 81 different polyamide molecules before coming up with five that best satisfied the prerequisites for its nylon synthetic fiber. And Thomas Edison explored 1,600 different materials before embracing the carbonized filament used in his first incandescent lamps -- a solution displaced later by tungsten filaments.

Less well known is the history of one of the 20th century's most important inventions, the integrated circuit.[11] Recognizing the desirability of packing many more transistor functions into a given cubic volume, the U.S. military services issued a dozen parallel R&D contracts to induce a solution. None succeeded, but seeing the demand for such a product, two companies, Fairchild and Texas Instruments, developed complementary solutions to the integrated circuit concept. The predecessor company to Fairchild had made numerous unsuccessful efforts to win one of the military contracts to support its work, but its staff had to go forward with Fairchild's funds and achieve a winning concept.[12]

Uncertainties in Pharmaceutical Discovery and Testing

The essential rationale for parallel paths strategies depends upon two conditions: (1) uncertainty about the correct solution among numerous possible approaches to a technological challenge; and (2) the desirability of achieving the rewards from solving the problem earlier rather than later. The second mandate is clear in pharmaceuticals: effective new drugs are profitable to

10 See Baxter (1947), pp. 433-436.
11 See Scherer (1996), pp.203-204.
12 From a conversation by co-author Scherer with Victor Jones, a member of the Schockley Semiconductor Laboratory staff and later professor of solid state physics at Harvard University.

their originators and even more valuable to the population whose ills they alleviate. The first condition is readily verified. The development of a new drug is typically characterized by a series of activities -- first discovery of promising molecules, then testing for safety in animals, and then increasingly expensive "phases" in which safety is first explored with human patients (Phase I), then early indications of therapeutic efficacy are sought through small-scale human trials (Phase II), and finally, statistically reliable proof of efficacy and safety is sought through Phase III trials involving hundreds to thousands of patients. As these phases are pursued, uncertainties decline.

At the discovery phase, it is not uncommon for only one molecule in one hundred, or even more, to reveal enough promise to be carried into human testing. Uncertainties ebb only as the process continues. Studies by DiMasi et al. (2003, p. 162) reveal that in recent experience, only 21 percent of the drug candidates tested in Phase I on average survive all three phases of testing to receive regulatory approval for general therapeutic use in the United States. The highest attrition rate is at Phase II, from which only about 44 percent of target molecules carried into that phase progress further. And of the roughly 21 percent of drugs that survive all three testing phases, only about one-third achieve sufficient commercial sales and profits to pay back the capitalized value of their R&D investments. See Grabowski, Vernon, and DiMasi (2002). Thus, there is substantial uncertainty as to whether any specific drug candidate is in fact therapeutically effective and whether successful drugs can achieve sufficient commercial success in the market to be profitable.

There is, to be sure, an alternative to a strict parallel paths strategy in coping with R&D uncertainty -- the so-called series strategy. With the latter, investment is directed to one set of options (or an initial set in parallel), and if that thrust fails, additional options are pursued sequentially until success is achieved. Given uncertainty, a pure series strategy option usually takes much longer than a parallel paths strategy. If the benefits conditional upon R&D success are

substantial, and if, as in drug testing, time lags are appreciable, waiting until success is achieved through a sequential series of R&D thrusts is economically unacceptable.

A Simple Example

At this point, we illustrate a relatively simple parallel-only example, adapted from Scherer (1966, 2007). We assume that decision-makers are unable to discern *ex ante* which of diverse contending molecules has a higher probability of success, i.e., single-approach success probabilities P_S are assumed homogeneous.[13] The probability of success for the aggregation of all N parallel approaches is P_{SN}, or 1 - $(P_F)^N$, where P_F is the probability of failure on a single approach (= 1- P_S) and N is the number of parallel approaches. The optimal strategy depends not only upon success probabilities but also crucially on the benefits, or in the case of private firms, quasi-rents, i.e., the surplus of annual sales revenues over variable production and distribution costs, attainable when success is achieved. We further assume that these quasi-rents Q(t) continue over time from the first year T_S after at least one successful molecule is approved to a future time horizon H. Future quasi-rents must of course be discounted to present value at a discount rate r. The decision-maker therefore chooses the number of paths N expected to maximize the surplus of discounted quasi-rents minus R&D costs, where the latter is N times the cost of a single approach C(RD):

$$(1)\quad \text{Max} \quad \int_{T_S}^{H} P_{SN}\, Q(t)\, e^{-rt}\, dt - N\, C(RD).$$

13 Significantly differing a priori success probabilities for alternative approaches tilt one's strategy in the series direction. See Scherer (1966). In a homogeneous-probability analysis lacking the Phase III time lags assumed here, Scherer (2007) shows that combining parallel with series strategies tends to yield higher profits, e.g., by roughly 20 percent in a low success-probability case, with the number of paths explored per period declining by as much as one-half. However, the total number of paths planned ex ante for exploration in this case, conditional upon no early success, tends to be higher than in the all-at-once case.

The model was evaluated for five diverse probabilities of single-approach success, ranging from 0.01 (one in one-hundred, most closely approximating the situation in early pre-clinical drug research) to 0.3, which approximates the historical odds of emerging from Phase I and Phase II clinical trials with a molecule that warrants further (more expensive) Phase III testing. To repeat, it is assumed that all approaches have the same a priori success probability expectation.

Numerical solutions for this model are graphed in Figure 1. To approximate most closely conditions in Phase II clinical testing, Figure 1 assumes that testing costs for a single approach are $50 million, assumed (oversimplifying) to be incurred in a single year.[14] If success is achieved, further Phase III tests must be conducted, with a probability-weighted expected cost of $P_{SN}\ C_3$ discounted to time 0. That Phase III cost C_3 is assumed here to be $200 million. Benefits begin flowing in at the conclusion of Phase III tests, assumed to be at t = 5 and continue for 14 years out to year 19. With this modification, equation (1) above includes an additional term -200 P_{SN}. The horizontal axis in Figure 1 measures the depth of the realized quasi-rent stream. Quasi-rents range in Figure 1 from $50 million per year to $5 billion per year -- the latter figure somewhat below the quasi-rents realized by the best-selling drug in history, *Lipitor*, in 2011. Again, benefits continue to accrue at a constant level for 14 years, i.e., to H = 19. A discount rate of 0.10 is used.[15] Shorter benefit inflow durations, higher discount rates, and higher R&D costs would mandate fewer parallel paths, all else being equal.

Figure 1 arrays the profit-maximizing parallel paths choices for various success probability and benefits stream values. For prospects with success probabilities of only 0.01, as in pre-clinical

14 In these numerical calculations, the model has been modified for the sake of realism from analogous versions presented in Scherer (1966 and 2007). The cost and timing assumptions are adapted from Scherer (2011).
15 To reflect the unusually low capital costs prevailing in the 2008-2012 period because of "quantitative easing," it has been adjusted downward by two to three points relative to the rates reported in earlier empirical studies.

drug discovery, profits are maximized by supporting as many as 150 parallel paths for the most lucrative prospects, assuming that a sufficient number of alternative equal-probability approaches can be identified. The profit-maximizing solution is highly sensitive, however, to the depth of the quasi-rents stream.[16] With success probabilities of 0.3, at the other extreme, from two paths (at annual quasi-rent flows of $100 million) to 14 parallel paths are warranted, depending upon the depth of the quasi-rent stream.[17]

Actual Evidence

In this section, we consider whether the leading pharmaceutical companies actually support anything like the degree of parallelism in R&D suggested as profit-maximizing by the analysis above. For this purpose, we reviewed the portfolios of Phase II and Phase III clinical trials that were ongoing during 2009 and 2010 for five leading U.S. pharmaceutical firms.[18] The trials were classified by narrowly-defined disease areas such as, for example, colorectal cancers, prostate cancer, depression, or epilepsy. Modifications and combinations of approved molecules along with vaccines were included. Parallelism was recorded when a company had more than one molecule in trial for the same narrowly-defined disease.

The results are summarized in Table 2. Altogether, 12 of the 83 Phase II trials, or 14.5 percent, were characterized by some degree of parallelism at the company level. Given an historical probability of roughly 0.3 that a molecule carried into human testing would transition from Phase II to Phase III trials, one might expect from Figure 1 parallelism of from 2 to 14 molecules per company per disease. Fifteen of the 79 Phase III trials, or 19 percent, exhibited some parallelism at

16 Note the truncated payoff curve, reflecting the fact that with such a low success probability, prospects yielding annual quasi-rents of less than $1.15 billion have negative expected profits.

17 With a quasi-rent stream depth of $75 million per year, a single path is barely profitable.

18 The data source is www.clinicaltrials.gov.

the company level. Although the odds of success are much higher at this stage, the degree of parallelism is again surprisingly modest. In both Phase II and Phase III trials, the Eli Lilly Company had the highest degrees of parallelism, 43 percent and 54 percent respectively. [19] From Table 1, one can see that Lilly had no significant recorded mergers between 1989 and 2011.

Clearly, the leading U.S. "Big Pharma" companies are not pursuing anything like the degree of parallelism suggested by our earlier analysis. It is of course possible that they are following more sophisticated parallel-plus-series strategies, although that seems too fragile a reed to explain the large disparity between theory and practice. We reach that conclusion because simulations with assumptions similar to those made in Figure 1 suggest a high optimal degree of parallelism even when series variants are added.[20] Higher cost or much lower benefit expectations from those assumed in Figure 1 could also alter companies' behavior. [21] It is also possible that company therapeutic candidate "libraries" contained too few promising molecules to warrant the degree of parallelism implied in Figure 1.

However, an alternative behavioral hypothesis cannot be ruled out: that companies fail to appreciate the full merits of parallel paths and/or view parallelism as a form of wasteful "duplication." That such a misperception of strategic options existed in the U.S. Department of Defense was asserted in an early and influential analysis that was a forerunner to the formal modeling of parallel paths strategies by economists. Hitch and McKean (1960, p. 249) argued that, given the technical and strategic uncertainties pervasive in military weapons R&D, one of the most important "pitfalls" in defense programs was "too little 'duplication'" or parallelism of R&D

19 We were puzzled by the low total number of Lilly Phase II trials relative to its Phase III count. Our research assistant suspected reporting gaps but was unable to find any.

20 See Scherer (2007).

21 As we shall stress later, quasi-rent distributions are highly skew after actual market experience is gained, and outcomes on the right-hand-side of the Figure 1 scale are rare. At the other extreme, clinical testing would seldom be pursued for projects with very low quasi-rent expected values. Ex ante, the distribution of quasi-rent expectations is likely to be less skew and centered on the left-hand third of Figure 1's horizontal axis.

approaches, with "duplication" put in quotation marks because duplicative programs were often criticized by members of Congress and others as wasteful. For managers to shun "duplication" when it is in fact an optimal strategy under uncertainty would therefore not be surprising.

The portfolio-pruning and cost-cutting practices that often follow a merger could be one reason why parallelism in pharmaceutical companies' clinical testing programs is so low. When a merger occurs, it is common for managers to analyze the R&D portfolios of the combined companies and eliminate those they see as "duplicative."[22] Following its merger with Wyeth, Pfizer closed one laboratory, downsized at least one other, and reduced its 2011 R&D spending by nearly 20 percent relative to the two firms' aggregate 2008 levels, with further cuts anticipated.[23] Merck, on the other hand, held its total spending roughly constant in the wake of its Schering-Plough acquisition.

That mergers do not yield more new drug approvals and may well reduce them is argued by a staff economist at Eli Lilly & Co., shown in Table 1 to be relatively merger-averse and in Table 2 to be one of the most aggressive parallel paths users. See Munoz (2009). On Lilly's stated reluctance to rely on mergers for new products, see the message of its CEO, Sidney Taurel, in the company's 2002 annual report (p. 2) .[24] Through regression analysis, Munos (2009) demonstrates that individual firms' cumulative new drug approvals rose more or less linearly over time, whether or not firm size had been enhanced by mergers. In a more focused analysis, he found that for larger companies, new drug approvals did not increase and may actually have declined slightly following substantial mergers. For smaller companies, on the other hand, there was a modest increase in the

22 This is explicitly suggested by John L. LaMattina (2011, p. 559), former president of Pfizer Global Research.

23 From company annual reports. See also Peter Elkind and Jennifer Reingold, "Inside Pfizer's Palace Coup," *Fortune*, August 15, 2011, pp. 76-91.

24 In a contemporary televised interview no longer available to us, Mr. Taurel expounded at length on his annual report statement that "all the evidence continues to show that such combinations do not create sustained value for shareholders."

average number of new molecules approved following a merger.

Industry-Level Analysis

The rationale of Figure 1 applies not only at the level of individual firms optimizing their R&D decisions but also at the level of the entire pharmaceutical industry. If there were a conscious "invisible hand" guiding the industry's investments, that decision-maker would implement enough parallelism of aggregate R&D approaches in any given therapeutic area to maximize the discounted surplus of benefits over R&D costs. For a planner concerned with society's well-being, however, the benefits included in this maximization process would be those accruing to all participants in the economy, and not simply the profits of individual firms.

It is universally accepted that the society-wide benefits from research and development tend to exceed private benefits realized by the R&D-performer alone.[25] For pharmaceuticals in particular, Frank Lichtenberg (2003) has estimated from a study of longevity effects that the social rate of return on pharmaceutical R&D approximates 68 percent per annum, assuming the value of a life-year saved to be $25,000. This value is roughly six times the private return (i.e., the return realized by specific drug-developing firms) estimated by Grabowski, Vernon, and DiMasi (2002). Recognizing that his life-year value assumption might be considered too high, Lichtenberg argues that an omitted assumption on the opposite side -- that new drugs improve the quality of life and individuals' productivity -- makes his social return estimate if anything conservative. To the extent that social returns exceed private returns, all else equal, the amount of parallelism sustained at the industry wide level should from the logic of Figure 1 be even greater than the individual company

25 For early cross-industry empirical results, see Mansfield (1977), who found social returns to be approximately twice private returns. See more generally Hall et al. (2010).

profit-maximizing level -- that is, the optimum shifts to the right on any given success probability curve.

That pharmaceutical companies are indeed pursuing research paths that are parallel to those of their rivals is suggested by the findings of DiMasi and Paquette (2004). They reported that 72 first-in-class drugs approved in the United States between 1960 and 1998 were followed by at least 235 drugs in the same narrow therapeutic categories by the year 2003, many emerging too soon to be influenced by the first-in-class molecules' success.

On the other hand, a further analysis of the data summarized in Table 2 reveals only modest pursuit of parallel paths toward a single disease in the combined efforts of our five subject companies. For Phase II, 55 narrowly-defined disease targets were identified. Ten were being pursued by two of the five subject companies; and two (Type II diabetes and rheumatoid arthritis) by three of the five. For Phase III, 52 targets were counted. Six entailed tests from two companies among our five; one (Type II diabetes) from four companies. Dividing the total number of multi-company investigations (not counting within-company parallelism) by the number of targets, one obtains a parallelism measure across the five companies of 1.25 for Phase II and 1.19 for Phase III. Although additional parallelism was undoubtedly underway among the many companies for which data were not compiled, this again reveals less parallelism than our Figure 1 theoretical analysis suggests.

Whether the degree of parallelism at the industry-wide level is too much or too little cannot be determined conclusively from the available evidence.[26] What is clear, however, is that when a major merger occurs, the number of independent sources of technological initiative is reduced, perhaps appreciably. And given Munos' evidence (2009) that mergers have not on average increased large companies' new product introductions, that lessening of initiative diversity most likely leads to

26 See Scherer (2010), pp. 562-569.

fewer parallel paths pursued and slower rates of pharmaceutical innovation.

This analysis suggests another important consideration. Since the discovery of gene-splicing techniques by Stanley Cohen and Herbert Boyer in the 1970s, the structure of drug research and development has been revolutionized. Hundreds of new "biotech" companies, most of them small and university-linked, have been established.[27] Although they also work on other applications, their principal emphasis has been the discovery and synthesis of new biological agents, usually called "large molecule" drugs, for possible use against a wide array of diseases. Between 1982 and 2011, 12.5 percent of the 705 new molecular therapeutic entities approved by the U.S. Food and Drug Administration were characterized as biologicals, with a rising trend over time.[28]

But there is a problem. Few biotech companies are large enough and have sufficient experience to carry their discoveries through complex and costly clinical testing and regulatory approval hurdles. Nor do they have the marketing capability needed to bring their approved drugs swiftly into broad medical use.[29] For the most part, they rely on much larger pharmaceutical companies to finance and conduct clinical testing and to market the drugs once they have received regulatory approval. This is achieved sometimes through a license agreement and sometimes through outright acquisition of the biotech pioneer by a larger and better-established drug company.[30] In either case, whether or not to assume responsibility for a new biological substance is a decision fraught with nearly as much uncertainty and financial risk as the decision to conduct

27 See Pisano (2006), especially pp. 100-109.
28 The data are presented graphically in Scherer (2011).
29 An example is seen in the history of Amgen, thus far the most profitable of new biotech companies. When it developed its revolutionary red blood cell-enhancing drug Epogen, it was able quickly to build a sales force marketing the drug to the small number of dialysis centers spread throughout the United States, roughly half of them subsidiaries of a single company. But it lacked the sales force needed to present the drug before the much larger number of hospitals and clinics treating cancer patients. As a result, it chose to license Epogen (under the alternative name Procrit) to Johnson & Johnson for use in cancer treatments.
30 See Comanor (2007).

clinical trials for its own "small molecule" candidates.[31] When mergers reduce the number of well-established pharmaceutical companies able and willing to provide complementary testing and marketing, they presumably also reduce the probability that some company will say "yes" and accept responsibility. New drugs may be lost.

To be sure, biotech startups might arrange alternative means to finance the substantial expenses associated with clinical testing, and indeed, some have succeeded.[32] A few venture capital firms have chosen also to provide financial help.[33] Although the logic of comparative advantage strongly favors "Big Pharma" companies in managing clinical tests and marketing as well as in finance, there are independent companies that contract to manage complex clinical testing programs.[34] Thus, the path to market for inventive biotech startups is not unequivocally blocked. But it is also not easy, and it has been made harder as the number of "Big Pharma" companies to whom the startups can turn for support declines in the wake of major mergers.

Optimal Portfolio Scope

Pursuing parallel research paths helps ensure that, when several uncertain R&D prospects are available, at least one will yield a technical success. But there is another dimension to uncertainty. Depending upon the market served and timing, some successes are much more profitable than others. Indeed, the distribution of payoffs, measured as the discounted present value of quasi-rents gained by FDA-approved new drugs, has been shown by Grabowski and Vernon (1990) to be quite skew. In their seminal analysis, the top ten percent of new drugs by number were

31 That success rates on biologicals have at least initially been higher than for small-molecule drugs is shown by DiMasi and Grabowski (2007).
32 That many new large molecules are accorded "orphan" status by the Food and Drug Administration, permitting less costly testing, also helps here.
33 On a Boston venture capital company that had raised $800 million to support 25 biotech startups, see Kirsner (2012). But for a skeptical view on venture capital support, see Primack (2011).
34 Indeed, one company, Quintiles, both manages clinical tests under contract and had as of May 2012 provided $2.4 billion in financing for other companies' efforts. Www.quintiles.com/capital.

found to capture 55 percent of total sample discounted quasi-rents. Their focus was approved drugs. We know from parallel studies that only 20 to 25 percent of the molecules carried into clinical trials emerge as approved drugs. Since drugs that are not approved presumably yield no profit returns, the top ten percent of drugs approved is roughly 2.5 percent of the drugs investigated clinically, and those 2.5 percent yield 55 percent of the ultimate returns.

To explore the logic of optimal portfolio choice under such skew-payoff conditions, a "dartboard" experiment was conducted.[35] The selection of R&D projects was analogized to throwing darts at a dartboard, whose 100 cells represented the diverse payoffs contingent upon research and marketing success. The distribution of cells or outcomes was log normal and hence skew, with the most lucrative 2.5 percent of "hits" accounting on average for 53 percent of total payoffs -- a close approximation to the Grabowski and Vernon results. The exact payoff function was:

$$(2) \quad D(P) = kX^{N(0,1)},$$

where N(0,1) is a random variable distributed normally with mean of zero and standard deviation of 1, D(P) is the payoff function, k and X are scaling parameters, and X was set at 10 and k at 1000 (e.g., dollars, multiplied by whatever further scaling parameter is suited to reflect pharmaceutical market realities).

Choosing R&D projects was analogized to throwing darts at the matrix of potential payoffs, with the location of "hits" randomly and independently distributed across the 100 cells. R&D costs per "throw" were also varied systematically, from zero to $12,000. Under conditions of certainty (e.g., perfect aim), the decision-maker would throw a single dart at each cell for which the payoff

35 See Scherer (2007).

exceeds the cost of the throw. With the assumed log normal distribution, the average number of perfect-aim 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

When costs are zero, dart-throwing with perfect aim continues until all hundred cells (each with at least a small positive payoff) are covered.

To achieve reasonably general results in the face of widely varying payoffs, 40 full random-aim experiments were carried out.[36] For each experiment, a new set of 100 payoffs distributed according to equation (2) was created using a random normal variable generator. As expected under such skew-distributed payoff conditions, 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; and the mean among the 40 experiments' maxima was $334,532. At the other extreme, many payoffs were minimal. The average payoff per throw among all payoffs across 40 experiments was $7,032.

Figure 2 summarizes the results for the 40 complete experiments, with the number of trials per sub-experiment incremented by discrete intervals from 5 to 100 (horizontal axis). The values

36 In the Scherer (2007) version, only 10 experiments were conducted.

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 20 throws to more than 100 at zero R&D cost per throw.

At low R&D costs -- $4,000 per trial (throw) or less -- average net payoffs are 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 cost of $6,000 per trial, two local maxima emerged -- one with 20 throws and an average net payoff of $120,650, and a maximum maximorum at 50 throws with an average net payoff of $149,829 after deducting the $300,000 total R&D cost per experiment.[37] 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.

In sum, given the kinds of value uncertainties pharmaceutical developers face, maintaining a substantial portfolio tends to maximize profits. The size of the optimal portfolio falls with increases in R&D costs, all else equal, dropping to as few as 20 trials when inter-firm competition is so vigorous that aggregate industry profits are driven to only a normal rate of return.[38]

To be sure, the optimal number of trials hinges on our assumption that the payoff matrix contains exactly 100 payoff possibilities or cells. In reality, the number of plausible opportunities, both within a given therapeutic target area (i.e., with the pursuit of parallel paths) and across all areas, could be larger or smaller. From the data underlying Table 2, it can be determined that the five large U.S. companies studied were pursuing 52 Phase III disease targets in total, or on average 10.2 targets per company, with four of those targets pursued under parallel paths.

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37 This duality results from the extreme skewness of outcomes even with replication across 40 experiments. The 20-throw experiments were apparently unusually lucky. Asymptotically, a single optimum would be expected.

38 On the rationale of such a "rent-seeking" equilibrium, see Scherer (2010), pp. 562-566.

Tapping a much more extensive confidential data set for the years 1960-1990, Coburn and Henderson (2001) found that their ten pharmaceutical company respondents supported in the average year from 1 to 42 active projects, with a mean of nearly 16. "Project" in this context was defined as a clinical development and testing effort in which at least $1 million was spent. In a multiple regression analysis, they found that the more "projects" a respondent company sustained -- i.e., the broader the scope of the company's R&D effort -- the higher was the probability that any given project would succeed in receiving marketing approval. No similar significant relationship was found with respect to the total magnitude or scale of the company's R&D spending. However, in their main publication, the authors did not report tests for nonlinear changes in the relationship. In an earlier paper apparently drawing upon the same data set, Henderson (1994) showed that the scope - success relationship was decidedly nonlinear when success is measured by the number of patents received per development program.[39] The peak output of patents per program was achieved at between six and eight programs, with patents per program declining by roughly half as the number of programs increased from between six and eight to 20. Although the authors do not directly draw the inference, it would appear that too rich a portfolio -- i.e., too many pots boiling on the R&D stove -- somehow reduced innovativeness. Whether excessive scope resulted from mergers or other managerial causes was not explained. But the results suggest caution in interpreting our dartboard experiment results, if indeed too many "throws" on different kinds of targets -- not parallelism per se -- reduce R&D productivity and hence the payoff probabilities assumed in the experiment to be given.

39 Patents are a better measure of output in pharmaceuticals, where the average number of patents underlying approved new drugs is on the order of three and patents are considered quite valuable, than in fields such as information technology, where a product is often covered by thousands of patents. See Scherer (2010), pp. 552 and 560-56. See also Comanor and Scherer (1969).

Conclusions

Our conclusions are suggestive rather than definitive. There are reasons rooted in the logic of uncertainty and parallel paths strategies to believe that large mergers adversely affect R&D investment and the probability that new drugs will be created. There is also some evidence that parallel (read pejoratively, "duplicative") paths are pruned in the wake of mergers. With fewer centers of initiative and decision-making, the chance that new technological prospects will gain large-scale support is probably reduced. Big Pharma mergers also restrict the number of independent decision-making centers able and willing to carry the creative efforts of small biotech companies into the expensive clinical development and marketing stages. To be sure, these conclusions are proposed as possibilities rather than proven phenomena. Our analysis nevertheless provides support for the hypothesis that recent mergers have contributed to the observed decline in the rate of pharmaceutical innovation.

REFERENCES

William Abernathy and Richard Rosenbloom, "Parallel Strategies in Development Projects," Management Science, vol. 18 (June 1969).

James Phinney Baxter, Scientists Against Time (Little-Brown, 1947).

William S. Comanor, "The Economics of Research and Development in the Pharmaceutical Industry," in Frank Sloan and C.R. Hsieh, eds., Pharmaceutical Innovation, Cambridge University Press, 2007, pp. 54-72.

William S. Comanor and F. M. Scherer, "Patent Statistics as a Measure of Technical Change," Journal of Political Economy, vol. 77 (May/June 1969), pp. 392-398.

Iain M. Cockburn and Rebecca Henderson, "Scale and Scope in Drug Development: Unpacking the Advantages of Size in Pharmaceutical Research," Journal of Health Economics, vol. 20 (2001), pp. 1033-1057.

Joseph DiMasi, Ronald Hansen, and Henry Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," Journal of Health Economics, vol. 22 (2003), pp. 151-185.

Joseph A. DiMasi and C. Paquette, "The Economics of Follow-on Research and Development," PharmacoEconomics, vol. 22 (2004), pp. 1-14.

Joseph DiMasi and Henry Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?" Managerial and Decision Economics, vol. 28 (2007), pp. 469-479.

Henry Grabowski and John Vernon, "A New Look at the Returns and Risks to Pharmaceutical R&D," Management Science, vol. 36 (July 1990), pp. 804-821.

Henry Grabowski, John Vernon, and Joseph DiMasi, "Returns on Research and Development for 1990s New Drug Innovations," Pharmacoeconomics, vol. 20 (2002), pp. 11-29.

Bronwyn Hall, Jacques Mairesse, and Pierre Mohnen, "Measuring the Returns to R&D," in Hall and Nathan Rosenberg, eds., Handbook of the Economics of Innovation (North-Holland: 2010), Chapter 24.

Rebecca Henderson, "Managing Innovation in the Information Age," Harvard Business Review, January-February 1994, pp. 100-105.

Charles J. Hitch and Roland McKean, The Economics of Defense in the Nuclear Age (Harvard University Press: 1960).

Scott Kirsner, "Venture Firms with a Twist," Boston Sunday Globe, June 17, 2012, p. G1.

John L. LaMattina, "The Impact of Mergers on Pharmaceutical R&D," Nature Reviews /

Drug Discovery, vol. 10 (August 2011), pp. 559-560.

Frank Lichtenberg, "Pharmaceutical Innovation, Mortality Reduction, and Economic Growth," in Kevin Murphy and Robert Topol, eds., Measuring the Gains from Medical Research (University of Chicago Press: 2003), pp. 74-109.

Eli Lilly and Co., Annual Report, 2002.

Edwin Mansfield et al., "Social and Private Rates of Return from Industrial Innovations," Quarterly Journal of Economics, vol. 91 (May 1977), pp. 221-240.

Bernard Munos, "Lessons from 60 Years of Pharmaceutical Innovation," Nature Reviews / Drug Discovery, vol. 8 (December 2009), p. 959-968.

Richard R. Nelson, "Uncertainty, Learning, and the Economics of Parallel Research and Development," Review of Economics and Statistics, vol. 43 (November 1961), pp. 351-368.

Merton J. Peck and F. M. Scherer, The Weapons Acquisition Process: An Economic Analysis (Harvard Business School Division of Research: 1962).

Gary Pisano, Science Business: The Promise, the Future, and the Reality of Biotech (Harvard Business School Press: 2006).

Ziv M. Preis, "The Incentive Theory of Patents in Action," privately published Harvard Law School doctoral thesis (September 2005).

Dan Primack, "Why You Should Blame Wall Street for Pharma's Startup Problem," Fortune, December 12, 2011, p. 82.

F. M. Scherer, "Time-Cost Trade-offs in Uncertain Empirical Research Projects," Naval Research Logistics Quarterly, vol. 13 (March 1966), pp. 71-82; reprinted in Innovation and Growth: Schumpeterian Perspectives (MIT Press: 1984), Chapter 2.

F. M. Scherer, Industry Structure, Strategy, and Public Policy (HarperCollins:1996).

F. M. Scherer, "Parallel R&D Paths Revisited," John F. Kennedy School of Government working paper RWP07-049 (September 2007).

F. M. Scherer, "Pharmaceutical Innovation," in Bronwyn Hall and Nathan Rosenberg, eds., Handbook of the Economics of Innovation (North-Holland: 2010), Chapter 12.

F. M. Scherer, "R&D Costs and Productivity in Biopharmaceuticals," John F. Kennedy School of Government working paper RWP11-046 (2011), forthcoming in A.J. Culyer, ed., The Encyclopedia of Health Economics.

Dava Sobel, Longitude (Walker:1995).

Table 1
Recent History of Large Pharmaceutical Mergers
(Survivors Are Ranked by 2010 Worldwide Sales)

1. Pfizer
   - 2009: Acquired Wyeth (which resulted from 1994 merger of American Cyanamid and American Home Products).
   - 2003: Acquired Pharmacia (which acquired Upjohn in 1995).
   - 2000: Acquired Warner-Lambert.

2. Johnson & Johnson (no major mergers).

3. Novartis
   - 2011: Acquired Alcon.
   - 1996: Resulted from merger of Ciba Geigy and Sandoz.

4. Roche
   - 2009: Consolidated 1990 acquisition of Genentech.
   - 1995: Acquired Syntex.

5. Bayer (no major mergers).

6. Merck
   - 2009: Acquired Schering-Plough.

7. Sanofi-Aventis
   - 2011: Acquired Genzyme.
   - 1999: Name changed after merger of Rhone-Poulenc and Hoechst.
   - 1995: Hoechst acquired Marion Merrell Dow.
   - 1995: Rhone-Poulenc acquired Fisons.
   - 1990: Rhone-Poulenc acquired Rorer.

8. Glaxo SmithKline
   - 2000: SmithKline Beecham merged with Glaxo.
   - 1995: Wellcome merged with Glaxo.
   - 1989: Beecham merged with SmithKline.

9. Abbott (no major mergers).

10. Astra Zeneca
    - 1999: Zeneca Group merged with Astra AB.

11. Eli Lilly (no major mergers).

12. Bristol-Myers Squibb
    - 2001: Acquired duPont Pharmaceuticals.
    - 1989: Bristol-Myers and Squibb merged; name change.

Table 2
PARALLELISM IN FIVE LEADING U.S. COMPANIES' 2009-2010
CLINICAL TRIALS

	Number of Trials	Same Condition
Phase II		
Pfizer	15	2
Merck	31	3
Johnson & Johnson	14	0
Lilly	7	4
Bristol-Myers Squibb	16	3
Total	83	12
Percent Parallel		14%
Phase III		
Pfizer	12	2
Merck	25	2
Johnson & Johnson	21	2
Lilly	13	7
Bristol-Myers Squibb	8	2
Total	79	15
Percent Parallel	19%	

Source: ClinicalTrials.gov

Figure 1

Optimal Parallel Paths Choices

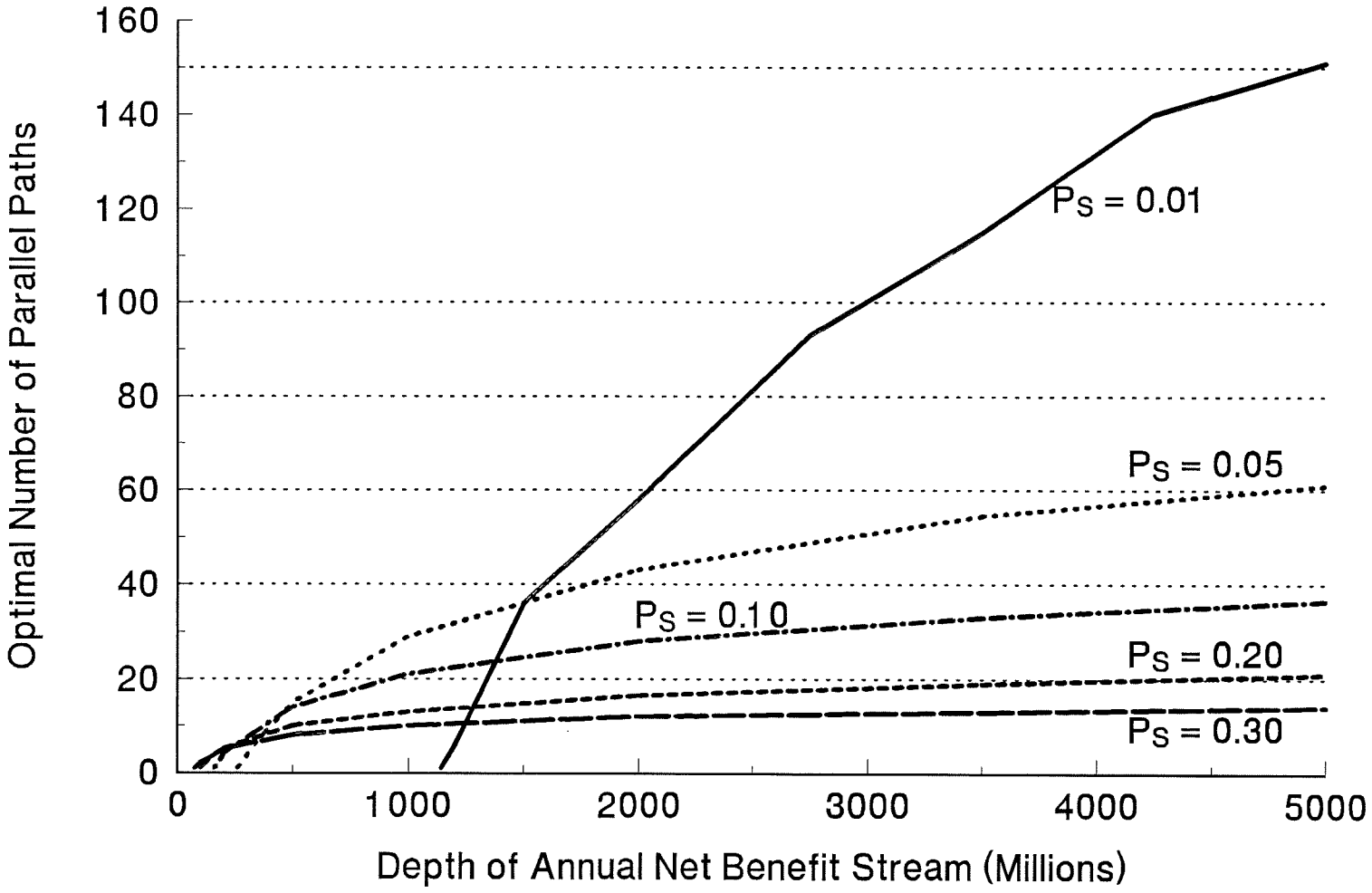

Figure 2

Average Net Payoffs from 40 Dartboard Replications