R&D Costs and Productivity in Biopharmaceuticals

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Faculty Research Working Paper Series

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December 2011
RWP11-046

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ABSTRACT

This article characterizes the activities required to launch a new pharmaceutical molecule into the market, summarizes studies that have attempted to pinpoint the research and development costs incurred per approved new molecule, and analyzes the various critiques levied against published R&D cost estimates. It finds that by any reckoning, R&D costs per approved molecule have risen sharply over time, most likely at a rate of approximately 7 percent per year after stripping out the effects of general economic inflation.

R&D COSTS AND PRODUCTIVITY IN BIOPHARMACEUTICALS

F. M. Scherer

Introduction

Substantial gains in human health and longevity have been achieved, especially since the 1930s, through the development and introduction into clinical practice of new pharmaceuticals, ranging inter alia from early antibiotics through anti-cholesterol agents to anti-cancer medicines. Most of the detailed development of new pharmaceutical entities has been conducted, at least in capitalist nations, by private enterprises, typically subject to detailed regulation by government agencies that monitor clinical testing activities and determine whether a proposed new drug is safe and efficacious enough to permit marketing. The pharmaceutical industry is one of the most research-intensive of all private industries. During the early years of the 21st century, however, there was evidence of sharply rising R&D costs underlying the average new pharmaceutical entity introduced into commercial use and hence reduced research productivity. This article explores the evidence and the issues, with a focus mainly on the United States, which has played a leading role in drug development and on which the most complete data are available.

Quantitative Overview

Figure 1 presents an overview of inputs and outputs for the drug R&D process. The solid line traces input trends -- notably, reported R&D expenditures (right-hand scale, in billions of dollars) by members of the principal U.S. trade association, the Pharmaceutical Research and Manufacturers of America, i.e., PhRMA. The data have important limitations. They are adjusted to year 2000 average purchasing power levels using the U.S. gross domestic product price deflator, although R&D cost inflation (measured from U.S. National Institutes of Health studies) has probably proceeded somewhat more rapidly than general economy-wide price inflation. Most of the leading pharmaceutical producers are multinational firms, but Figure 1 includes only the R&D expenditures of PhRMA members within the United States. Counting overseas outlays of the members, many with home bases elsewhere, would add roughly 25 percent. Not all private-sector company pharmaceutical R&D outlays are made by PhRMA members. A particularly important exclusion is for biotechnology specialists, many of which do not publicly report their R&D outlays. Several biotech companies were members of PhRMA in 2008, so their data are included in the PhRMA tallies. But most joined only after incurring the R&D underlying successful drug developments, and it would appear that the reported PhRMA R&D totals were not recalculated backward to hold membership constant, in which case the addition of new members overstates actual growth rates. Recognizing these limitations, one can estimate from Figure 1 that inflation-adjusted R&D outlays grew between 1970 and 2007 at an average annual rate somewhat

below 7.4 percent.

<Figure 1 near here>

The dash-dash line in Figure 1 estimates the number of new molecular entities (NMEs) (left-hand scale) approved each year for prescription use in the United States. The count of new molecular entities includes new therapeutic organic chemical molecules -- the so-called "small-molecule drugs," excluding new uses of already-approved molecules and different formulations of pre-existing molecules, plus the typically much larger molecules derived by gene-splicing and related biological processes (but excluding vaccines, blood products, and the like). The large molecule drugs, conveniently called "biologicals," are also broken out for separate reporting with the dotted line in Figure 1, beginning with the first such new entry, a synthetic human growth hormone, in 1982. Because source counts vary, some estimation error cannot be avoided. It is clear with any set of definitions that the number of new drug approvals varies widely from year to year. The spike around 1996 is artificial, resulting from a sharp fee-induced reduction in the Food and Drug Administration's backlog of drugs awaiting approval. When that peak is redistributed over subsequent years, one finds a modest upward trend of about 2.1 percent per year.

With inflation-adjusted R&D expenditures rising at roughly 7.4 percent per year and the approval of new pharmaceutical entities increasing at only 2.1 percent year, it appears likely that the average R&D cost of new molecular entities has been rising over time.

The R&D Phases

The discovery and testing of potential new drugs follow a fairly regular sequence of stages characterized in Figure 2. The horizontal time axis is calibrated at zero for the year when testing in humans begins. The vertical axis smooths impressionistically annual spending levels in year 2000 dollars, approximating averages reported by DiMasi et al. (2003, p. 165) for drugs emerging mainly during the 1990s. The costs assumed are those of a project that goes all the way from preclinical work to regulatory approval. No adjustment is made for uncompleted phases, e.g., abandonments or failures. There is a long period in which basic and applied research seeks to find and/or synthesize new molecules and identify through theory and in vitro testing which ones might actually work in human beings. In the early years of active pharmaceutical research, the discovery process entailed mostly random "try every bottle on the shelf" search, but as scientific knowledge has advanced, theory has come to play an increasingly important role. Once a promising molecule has been identified, it is tested in animals for possible toxicity.

<Figure 2 near here>

If that hurdle is cleared, a stylized set of human testing phases begins, with appreciable attrition rates at each phase. In Phase I, the drug is administered to a typically small sample of humans to determine the safety of various dosages and in some cases to secure preliminary insight into whether the molecule can alleviate the target disease. If those tests yield promise, targeted Phase II tests for efficacy are conducted in larger cohorts. Success in Phase II is typically followed by much more extensive Phase III tests carefully designed with double blinds to infer at reliable levels of statistical confidence whether the drug is safe and effective relative to placebos or, less often, relative to the best-accepted approved drug in the relevant therapeutic category. Phase III tests, typically divided into at least two distinct protocols, may encompass from a few hundred human subjects (only for diseases with no known cures) to more than 10,000 individuals. If the results from Phase III are promising, the drug developer (usually a private pharmaceutical company) applies for marketing approval -- in the United States, for an NDA (new drug approval) issued by the Food and Drug Administration; and in Europe since 1995, to the European Medicines Agency. On average, only one-fifth to one-fourth of the small-molecule drugs entering Phase I testing emerge roughly eight years later with marketing approval. For biological therapies developed during the 1990s, the survival probabilities appear to be higher -- e.g., roughly 0.3 from a survey by DiMasi and Grabowski (2007) and even higher for the earliest approved biologicals, which mainly emulated naturally occuring substances.

The relevant regulatory agency may after approval insist upon additional tests to clarify remaining uncertainties, in which case, further trials continue into a Phase IV. Or the company developing the drug may seek to illuminate more exactly the differences between its drug and existing competitors, embarking on its own initiative into further Phase IV testing.

For wholly new vaccines (as compared to minor variants adapted annually to new strains of influenza) even larger human test samples are often needed. The basic problem is, once a subject acquires the target disease, it may be too late for vaccine administration. For preventative vaccines, tests are conducted on populations that might be afflicted in the future, and to keep trial periods within reasonable time bounds, given small probabilities that any given sample member will actually acquire the disease, samples numbering in the tens of thousands may be required to achieve acceptable levels of statistical discrimination along with detecting adverse reactions. To be sure, subjects might alternatively be injected with the target organism after vaccine administration, as was done for example during the 18th Century in the discovery of the first cowpox-based smallpox vaccine, but this approach violates medical ethics and is now avoided.

Estimating R&D Cost per Successful New Drug

Given this broad picture and its many variations, interest has focused on the productivity of research and development in yielding new pharmaceutical therapies

-- i.e., the cost per successful new molecule. There have been numerous quantitative investigations. The leading efforts, and those most highly cited in both the scientific and popular literature, have come from collaborating economists at Tufts University, the University of Rochester, and Duke University. See e.g. DiMasi, Hansen, and Grabowski (2003). Their methodology, which to minimize the proliferation of names will be called the Tufts University studies, enlisted deep cooperation from a handful of major pharmaceutical companies (in the most comprehensive recent effort, ten) operating in the United States. The investigators began by identifying a set of clinical testing programs undertaken by the cooperating enterprises on 68 so-called "self-originated" molecules first tested in humans between 1983 and 1994 . Their sample excluded "licensed-in" drugs whose early development was performed by companies other than the survey respondents. Once the molecules entered clinical testing, detailed data on individual test program costs and failure rates were obtained so that they could be aggregated into estimates of the average cost per successful molecule, i.e., the actual out-of-pocket cost of the ultimate successes, into which were loaded the probability-adjusted estimates of pre-clinical and clinical phase failure costs. If, for example, only one molecule out of five entering Phase I testing ultimately secured marketing approval, the cost of an average Phase I test, successful or unsuccessful, was multiplied by 1 / 0.2 = 5 to obtain the average Phase I success cost. Similar probabilistic adjustments were made for later stages. For the most recent of the comprehensive Tufts University studies, the estimated average out-of-pocket cost per successfully approved molecule, including the pro-rated costs of failed tests, all measured in year 2000 purchasing power levels, were as follows:

Pre-clinical	$121 million
Clinical testing	$282 million
Total cost per approved drug	$403 million

The mean clinical testing estimates, which are undoubtedly more reliable than pre-clinical estimates, can be compared with the analogous costs from three earlier studies summarized by Scherer (2010, p. 154), each adjusted to year 2000 purchasing power levels:

Source	Test Period	Average out-of-pocket cost per approved new drug
Mansfield	Late 1950s	$ 5.4 million
Clymer	Late 1960s	40.2 million
Tufts I	1970-early 1980s	65.7 million
Tufts II	1983-late 1990s	$282 million

It seems clear that the clinical R&D costs of new drugs have exploded over time. The particularly large multiplier between the estimates of Edwin Mansfield and

Harold Clymer is explained by the fact that after 1962, constrained by new and tougher legislation, the U.S. Food and Drug Administration enforced much more stringent rules for the evidence it would accept before approving new drug applications. We return to the sizeable increase between Tufts I and II subsequently.

The estimates of success probability-adjusted preclinical R&D costs by the Tufts group are more problematic. For the Tufts II sample, we see above, the mean value was $121 million, or 30 percent of total estimated mean cost per successful molecule. For the Tufts I sample (from the 1970s), it was $90 million (in year 2000 dollars), or 57.8 percent.

The striking reduction over roughly 15 years in pre-clinical cost shares, not explained by the Tufts researchers, is probably attributable to radical changes in the way new drugs have been discovered. The science of drug action in the human body advanced by leaps and bounds in the time interval separating the two studies, leading among other things to so-called "rational drug design" -- that is, the structured synthesis of molecules targeted to interact in particular ways with known receptors in the human body. (A detailed chart of biological pathways is revised and published periodically by the Boehringer-Ingelheim Co.; see Michal (1993) in the Further Reading.) Much of the research underlying such insights was conducted not in drug company laboratories, but in universities and hospitals supported by grants, most notably, from the U.S. National Institutes of Health. Between 1983 and 2000, the research budget of "NIH" rose from roughly $2.7 billion (at year 2000 GDP price levels) to $14.4 billion, or two-thirds of U.S. R&D outlays by PhRMA member firms in 2000. Additional research support came from the U.S. National Science Foundation and private philanthropic institutions. An unknown but undoubtedly substantial fraction of such outlays generated basic knowledge helpful in the design of new pharmaceutical entities and in many cases identified specific molecules eventually brought into clinical testing by private sector enterprises. See e.g. in the suggested readings Scherer (2010) and Stevens et al. (2011).

Also, the first drug synthesized using radically new gene splicing methods was introduced commercially in 1982, spurring the explosive growth of a new biotechnology industry, mostly in new companies initially financed by venture capital. Although 90 percent of the entities comprising the Tufts II sample were small molecules (as contrasted to biologics), it cannot be ruled out that the sample companies saved some pre-clinical R&D expenditures by building upon research done inter alia in biotech enterprises. However, DiMasi and Grabowski (2007) report quite similar constant-dollar R&D cost estimates for their Tufts II sample and a slightly later sample covering only biological entities.

Critiques

The Tufts estimates and their predecessors have been widely cited by pharmaceutical industry advocates to argue that drug testing is both risky and costly, and, with additional evidence, that government agencies ought not to intervene in pharmaceutical companies' controversial price-setting process (which in fact many national governments do through various price control mechanisms). Given this, the estimates have been criticized as biased and excessive. Diverse and conflicting critiques are found in Love (2003), Angell (2004), and Light and Warburton (2011). The criticisms have several foci.

Capitalization

More widely cited than the out-of-pocket averages presented above are estimates from the Tufts research of average drug discovery costs, capitalized to "present value" at the time of product approval to reflect the cost of capital tied up during the R&D period. In the 1983-late 1990s estimates presented above, for example, out-of-pocket costs were capitalized to the time of marketing approval at an implied 11 percent cost of capital. To illustrate, suppose that ten years before a new drug's approval date, e.g., at year -2 in Figure 2, out-of-pocket costs amounting to $5 million (with adjustments for failed trials) are observed. The capitalized figure becomes $5 million x ($1.11^{10}$) = $5 million x 2.59 = $12.97 million, which is the value incorporated into the capitalized R&D cost sums. Here 1.11^{10} is the amount to which one dollar grows over ten years at compound annual interest. Such adjustments are made for each year to take into account the "opportunity cost" of companies' investable funds on the assumption that if the money were not invested in R&D, investors could allocate it to other comparably risky assets that over time would yield 11 percent inflation-adjusted annual returns (derived from standard finance sources using the so-called Capital Asset Pricing Model). For years nearer the time of marketing approval, the adjustment is of course smaller; e.g., five years out, 1.11^{5} = 1.685 rather than 2.59. When these capitalization adjustments are made, among other things giving relatively greater weight to pre-clinical as opposed to clinical testing costs, the $403 million Tufts II average successful drug development cost reported above nearly doubles to $802 million. For the earlier Tufts I study, average out-of-pocket costs (pre-clinical plus clinical) rise in year 2000 dollars from $156 milion uncapitalized to $318 million capitalized.

This capitalization assumption, typically reported in the popular press without explanation, has been criticized by e.g. Light and Warburton (2011) on both conceptual and numerical grounds. To be sure, most estimates of investment outlays for research and development as well as physical facilities, advertising, and much else, are typically publicized in unadjusted form for the year of incurrence rather than with capitalization, and consistency in reporting practice would argue for avoiding capitalization, unless the rationale is clearly explained. Nevertheless, it is clear that R&D outlays do have opportunity costs, and in drug discovery and testing,

with their long time lags between outlay and the return of profits, the opportunity costs are more significant than for investments with quicker paybacks. Public controversy over the capitalization issue became sufficiently intense in the early 1990s that a specially created U.S. government agency study team focused on it, among other things obtaining consulting assistance from prominent finance theorists. Its report was in U.S. Congress, Office of Technology Assessment (OTA) (1993). The study group concluded (p. 7) that the three most important components of R&D investment are "money, time, and risk" and (p. 66) that "the practice of capitalizing costs to their present value in the year of market approval is a valid approach to measuring R&D costs...." Given the lack of public understanding, however, it would undoubtedly be good practice for journalists to report out-of-pocket costs along with capitalized cost estimates.

The higher the interest rate used in capitalization, the larger is the multiple between out-of-pocket and capitalized costs. Light and Warburton argue (2011, p. 41) that the 11 percent interest rate used by the Tufts group was too high, given that U.S. Government Office of Management and Budget guidelines in 2003 called for applying a 3 percent interest rate in evaluating public capital outlays. This criticism is clearly wrong. Governments like the United States (at least up to the year 2012) financed their deficits with what were widely considered "risk-free" bonds that indeed often bore quite low interest rates. But the common stock with which corporations are financed is riskier and bears considerably higher implicit interest rates. Addressing this issue, finance experts advising the U.S. Office of Technology Assessment found (p. 67) that the cost of capital (i.e., the implicit interest rate) for established pharmaceutical companies in the 1980s and early 1990s was on the order of 8 to 10 percent after stripping away inflation premia. They found too that R&D-intensive activities were more risky than ordinary corporate investments, calling for interest rate premia on the order of 4.5 percentage points, or approximately 13 to 14 percent over-all. Recognizing this, the 11 percent implicit interest rate used by the Tufts group appeared consistent with broader knowledge and perhaps even conservative for the time period covered.

Tax Benefits

Some critics have argued that tax savings realized by corporations as a result of their R&D outlays (treated as current expenses under prevailing tax accounting) ought to be deducted in estimates of what drug development costs. It is true that tax offsets exist. Considering first only the corporate income tax, when a corporation spends an incremental dollar on R&D, that dollar reduces its current pre-tax profits by a dollar (assuming profits to be positive), and at the 35 percent U.S. corporate income tax rate prevailing at the time of the most recent Tufts study, a savings of 35 cents is achieved. The problem with adjusting for this saving is that it applies for <u>any</u> incremental expenditure in a positive-income regime -- for the cost of hiring an additional worker, for the cost of fuel, for the cost of environmental cleanup activities, and so on. But to apply such adjustments for every expenditure

requires distinctions between optional and mandatory outlays and runs into the difficulty that, if every expenditure were treated as less costly than its out-of-pocket cost, expenditures could rise to exhaust the profits against which savings are claimed. Also, multinational pharmaceutical companies have been adept at shifting their reported profits to nations with low marginal income tax rates, so any attempt to offset R&D outlays by tax savings would have to cope with a multiplicity of savings rates.

A somewhat better case can be made for adjusting R&D outlays for tax benefits specific to R&D. These were of two main relevant forms. Under U.S. law since the 1980s, credits against income tax liability have been offered for increases in R&D expenditures relative to the amount expended in specified base years. The provisions of the law have varied from time to time, so adjustments would be complex. Because the credits apply only to incremental outlays above a base year value, it would be difficult to determine which outlays in a large R&D budget are incremental and which are within the no-credit baseline. Special 50 percent federal income tax credits have also been offered under U.S. law since 1983 for costs incurred testing so-called "orphan" drugs, i.e., those expected to serve small patient populations. Since the credits are targeted at specific molecules, adjustments to orphan drug R&D costs would be more feasible than adjustment for generalized tax savings. We return later to other complexities of estimating orphan drug R&D costs.

More generally, the genuine issues posed by capitalization and tax benefits are best judged in policy evaluations of pharmaceutical companies' aggregate net profitability, not with respect to specific drug discovery and testing cost estimates. There too issues arise, although they are beyond the scope of this essay. The Office of Technology Assessment study concluded (1993, p. 24) that established pharmaceutical firms' rates of return on net capital averaged two to three percentage points higher than their cost of capital, estimated to be roughly 10 percent after taxes. The OTA group refrained from rendering a clear value judgment as to whether such a premium was problematic, given the risks of new drug development and the desirability of attracting new investment.

Sample Representativeness

Without doubt the most compelling criticism of the Tufts methodology is that their samples may not have been representative of the entire drug development universe. For the Tufts II estimates, the unnamed product sample and cost data came from ten pharmaceutical firms, eight of them from the top 20 in terms of sales volume -- i.e., the representatives of what many call "Big Pharma." It is conceivable that the drugs chosen for development by those companies differed from those developed by smaller firms or even misrepresented the respondents' typical portfolios. In particular, with vast sales pipelines to fill, the companies may have emphasized candidates with a large sales potential -- i.e., with luck, the

"blockbusters." For example, drugs that address widespread health conditions and that are prescribed for chronic as contrasted to acute symptoms tend to have better sales prospects than those targeting relatively rare and/or acute conditions -- e.g., those with the mandate, "Take two tablets per day for ten days and if the symptoms persist, see your doctor." Higher sales prospects, both theory and statistical analyses reveal, induce more lavish R&D outlays. See Scherer (2010), pp. 560-564.

The testing strategies mandated by the Food and Drug Administration or favored by the companies may also have differed. For drugs that will be taken daily for years on end, regulators tend to be more wary of rare and/or cumulative adverse side effects and require larger samples to impart additional statistical confidence on what might otherwise be seen as clinical testing flukes. And for drugs alleviating chronic medical problems of long standing, new drugs will often have to compete with existing therapies that may arguably be less effective, but the differences are foreseen to be sufficiently small that tests are authorized not against placebos, but against established molecules, with unusually large clinical populations to obtain evidence bolstering marketing claims that the new drug is in fact superior to existing alternatives.

A case history at the opposite extreme is seen in the first drugs effective against HIV/AIDS, recognized as a threat by physicians only in the 1980s. The lethality of AIDS was so shocking, and its spread so rapid, that clinicians and regulators accepted major shortcuts to ensure that weapons against the disease were at hand. The first candidate, AZT (also known as Zidovudine), was approved by the Food and Drug Administration in March 1987 -- only 25 months after the start of human testing, breaking post-1962 speed records. Although comparative placebo tests were conducted, the decisive trial included only 282 patients, and instead of waiting to see whether or how long AZT recipients lived, FDA evaluated the drug's efficacy mainly on the basis of "surrogate endpoints" -- i.e., measures of retroviral levels in trial subjects' blood. Clinical trials were conducted jointly by Duke University, Burroughs-Wellcome, and the National Institutes of Health, with substantial financial support from the NIH. Another AIDS drug, Nevirapine, with the remarkable ability significantly to inhibit transmission of the disease from infected mothers to newborn children, was approved in June 1996 after trials spanning 76 weeks on a total of 549 patients, one branch conducted by the U.S. NIH in parallel with other tests by the drug's inventor, Boehringer-Ingelheim of Germany. See Love (2003).

The initial AIDS drug developments shared two distinguishing bureaucratic characteristics. For one, the early AIDS population was sufficiently small that the first therapeutic candidates were ruled at the outset to be "orphan drugs" -- i.e., mainly targeted toward conditions afflicting 200,000 or fewer individuals in the United States. Second, they were also accorded "priority" status by the Food and Drug Administration -- i.e., for molecules offering potentially major improvements over already marketed therapies, as distinguished from "standard" drugs yielding

more modest therapeutic gains.

As we have seen, private funds devoted to orphan drug testing have been accorded in the United States especially favorable tax status, and clinical testing support by Federal government entities is also common. Recognizing the possibly small market potential of orphan drugs, the Food and Drug Administration has tended to accept smaller clinical trial samples than for drugs targeting wider markets. Also, because of the tax implications, data are publicly available on the total amount spent for orphan drug testing. For 16 new orphan chemical entities approved in the United States between 1998 and 2000, the average clinical trial cost per approved orphan, pro-rating the costs of failed tests, was $34 million. See Love (2003, p. 7). This is far below the $282 million out-of-pocket for the most recent Tufts sample, the bulk of whose testing outlays occurred in years earlier and hence were less inflated than those gleaned by James Love. Although DiMasi et al. (2003) do not elaborate the point, the Office of Technology Assessment reported (1993, p. 232) that roughly two-thirds of orphan drug designations went to companies that were not PhRMA members.

Orphan drugs are also more likely to obtain priority rankings from the Food and Drug Administration than standard drugs. Thus, for new chemical entities approved by the FDA during the first five years of the 21st Century, 89 percent of the orphans had priority ratings, as compared to 38 percent for the standard drugs. Scherer (2010, p. 163). Since the early 1990s, the Food and Drug Administration has tended to process non-orphan priority drug approval requests more rapidly than standard requests. It is also possible that FDA demands fewer and less costly clinical trials for priority drugs, but on this the evidence is sparse. DiMasi et al. (2003, p. 172) report that in their Tufts II sample, the out-of-pocket clinical testing costs of priority drugs exceeded the average cost of standard drugs by a statistically insignificant amount. The difference was even smaller for capitalized costs, implying that test-to-approval lags were shorter for the priority drugs. DiMasi et al. suggest that priority drugs may have been more costly to test because they break newer scientific ground, requiring more learning-by-doing, and also (p. 172) because "firms have the incentive to do more wide-ranging and costly testing on drugs that have the potential to be both clinically and commercially significant." Whether this inference carries over to the non-orphan priority drugs tests of smaller companies is unknown.

An Independent Test of the Evidence

There are other fragments of evidence suggesting average out-of-pocket costs lower for drugs outside the Tufts sample than for in-group molecules. But now we advance to an alternative approach. Several authors, such as Adams and Branter (2005), have pursued more aggregative approaches to the problem of estimating drug development costs. Here I report the result of my own broad-brush approach. The methodology is simple: dividing annual counts of new therapeutic

entity approvals in the United States into the reported intra-United States research and development spending of PhRMA members. It is bound to be incomplete and inexact for at least four reasons. First, PhRMA's membership includes companies with a home base outside the United States, and by excluding overseas R&D outlays, the full costs of their drugs approved in the United States are certain to be underestimated. Second, many of the drugs approved in the United States come from non-PhRMA members, and while such firms' innovations are included in the denominator of cost/drug calculations, their R&D outlays are excluded from the numerator, again resulting in an underestimate. Over the years 2001-2005, the non-PhRMA share of approved new medical entities was 51 percent, implying a sizeable downward bias. Third, the R&D expenditures of PhRMA members are focused not only on developing and testing new molecular entities, but also testing to see whether existing molecular entities are effective against additional disease conditions, developing vaccines and other biological products, and reformulating inert binders that control the timing of a drug's release into the blood stream. And much Phase IV research undertaken by major pharmaceutical firms is aimed not at complying with regulatory agency mandates, but to strengthen evidence used in field marketing of already approved molecules. By excluding such projects from the denominator count, the cost per drug, new and old, is overestimated. And finally, as we have seen in Figure 2, the R&D expenditures underlying new entities precede by as much as a decade the date of approval. Lags must be accounted for, but are inherently variable.

Recognizing that perfection is unattainable, the following methodology was pursued. The Figure 1 time series of new molecular entity approvals for the years 1974 through 2007, including both small-molecule drugs and some biologicals (but not vaccines and the like) was used as the denominator of the cost calculation. Total reported R&D expenditures of PhRMA members in the United States were used, adjusted with the Gross Domestic Product deflator to constant year 2000 price levels, to measure costs. To reflect the fact that approvals lag the incurrence of testing costs, the R&D series was pre-lagged by four years relative to approvals, e.g., approvals in the year 2000 were related to 1996 R&D expenditures. This convention reflects in a crude way the central tendency of the outlay flow shown in Figure 2, with outlays peaking three years before approval but with early outlays weighted more heavily due to attrition.

The Tufts II analysis focused on drugs whose clinical test expenditures were mostly incurred between 1983 and 1999. Within that restricted sample of years, the computed average out-of-pocket cost R&D per lagged new molecular entity approved, using the methodology described above, was $306 million in year 2000 dollars (also used as the measuring basis for Tufts group's summary estimates). When the exercise was repeated without the inclusion of biological entities, the average was $390 million. The Tufts II estimate, including seven biologicals (10 percent of the sample) was $282 million. The difference is small, suggesting that for an intrinsically difficult measurement, the Tufts estimates are both credible and

perhaps even conservative.

For the full 1974-2007 molecular approval series, the average growth rate of constant-dollar R&D costs per molecule was found by regression analysis, which smooths year-to-year variations, to be 6.5 percent per year with biologicals included and 7.2 percent per year with them excluded. DiMasi et al. (2003, p. 151) estimated the growth rate between their Tufts I and Tufts II studies, spanning slightly shorter intervals, to be 7.4 percent. Again, the conclusion seems inescapable that there has been substantial growth in R&D costs per new approved molecule, or in other words, a decline in research productivity.

Reasons for Change

Several hypotheses vie to explain the apparently continuous increase in R&D costs per molecule approved. Despite advances in the technology of pre-clinical small-molecule screening, one might suppose that diminishing returns would set in after seven or more decades of active discovery, among other things forcing companies to focus on more difficult therapeutic targets. During the 1990s it was thought that the perfection of large-molecule gene-splicing techniques would reverse any such tendency and usher in a new golden age of pharmaceutical discovery. However, the observable changes thus far have been less than revolutionary.

There is definite evidence that clinical trial sizes have risen over time, partly as a result of tougher standards established by the U.S. Food and Drug Administration. Also, as individual therapeutic classes became more crowded, companies may have elected to increase sample sizes to improve the statistical significance of results touted in competitive marketing. For three therapeutic categories studied by the Office of Technology Assessment (1993, p. 145), average enrollment in Phase I through III clinical trials rose from 2,237 for drugs approved in 1978-1983 to 3,174 for 1986-1990 entities, implying a median year growth rate of 4.7 percent. The average number of subjects drawn into Phase IV grew much more rapidly, from 413 to 2000 [sic], or 21 percent per year. Using publicly available data, DiMasi et al. estimate (2003, p. 177) that average trial sizes in the 1980s and 1990s rose at a rate of 7.47 percent per year. In addition, the complexity of trials rose. DiMasi et al. report (2003, p. 162) from an outside data source that the number of procedures administered per trial subject increased between 1990 and 1997 by 120 percent for Phase I trials, by 90 percent for Phase II trials, and by 27 percent for Phase III trials. Weighting the phase growth percentages by the fraction of out-of-pocket costs incurred per phase, this implies an average growth of 50 percent in seven years, or 5.8 percent per year.

Clinical trials are mostly conducted in hospitals and similar medical centers. Over the period 1970 to 1990, the cost of a day of hospitalization in the United States rose at an average rate of 11 percent per year -- nearly twice the rate at which the

gross domestic product price index was increasing. It seems reasonable to assume that in-hospital test costs rose commensurately. There is also reason to believe that major hospitals view their clinical testing activities as a "profit center" and dump some of their soaring overhead costs onto the well-heeled pharmaceutical firms sponsoring clinical trials.

A more speculative hypothesis is that "Big Pharma" companies have allowed organizational slack to accumulate in their R&D activities, especially after numerous large-company mergers failed to achieve substantial increases in the output of new therapeutic entities. See Munos (2009), pp. 965-966. A correction against this trend may have begun in the second decade of the 21st Century as pharmaceutical giants such as Pfizer and Merck, acknowledging disappointment over the lagging productivity of their innovation efforts, cut back their R&D staffs in the wake of major new mergers.

Conclusion

In sum, the research and clinical testing costs underlying pharmaceutical innovations have risen greatly over recent decades to levels measured in the hundreds of millions of dollars per approved new molecule. The most widely publicized estimates of R&D costs, sometimes poorly understood, are consistent with alternative estimates. There would probably be less controversy over those estimates if more detailed data on sample composition were disclosed, but confidentiality constraints imposed in exchange for access to company microdata may preclude this. It is clear that clinical success may be achieved at substantially lower cost with alternative models of pharmaceutical development and testing, but embracing those alternatives requires streamlined regulatory and organizational approaches and sacrifices in the richness of the evidence on the basis of which physicians must make subsequent prescription choices.

Further Reading

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Figure 1

Trends in Newly Approved Molecules and R&D Spending

United States, 1970-2009

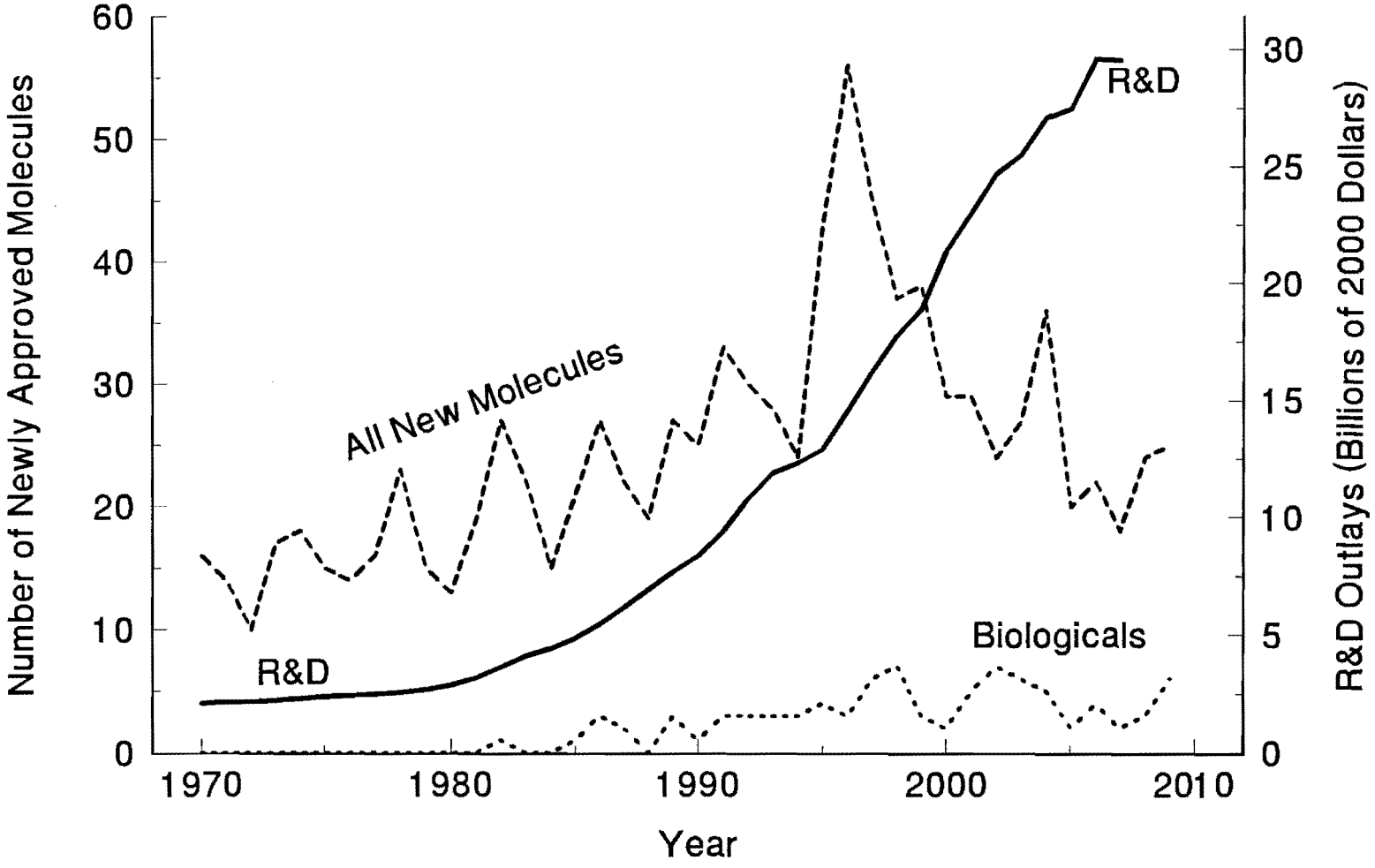

Figure 2

Schematic History of a Successful New Drug Development