Original Article

Demythologizing the high costs of pharmaceutical research

Donald W. Light[a,b,*] and Rebecca Warburton[c]

[a]Program in Human Biology, 450 Serra Mall, Building 20, Stanford University, Stanford, CA 94305, USA.

[b]University of Medicine and Dentistry of New Jersey, c/o 10 Adams Drive, Princeton, NJ 08540, USA.
E-mail: dlight@princeton.edu

[c]School of Public Administration, University of Victoria, Victoria, BC, Canada.
E-mail: rnwarbur@uvic.ca

*Corresponding author.

Abstract It is widely claimed that research to discover and develop new pharmaceuticals entails high costs and high risks. High research and development (R&D) costs influence many decisions and policy discussions about how to reduce global health disparities, how much companies can afford to discount prices for lower- and middle-income countries, and how to design innovative incentives to advance research on diseases of the poor. High estimated costs also affect strategies for getting new medicines to the world's poor, such as the advanced market commitment, which built high estimates into its inflated size and prices. This article takes apart the most detailed and authoritative study of R&D costs in order to show how high estimates have been constructed by industry-supported economists, and to show how much lower actual costs may be. Besides serving as an object lesson in the construction of 'facts', this analysis provides reason to believe that R&D costs need not be such an insuperable obstacle to the development of better medicines. The deeper problem is that current incentives reward companies to develop mainly new medicines of little advantage and compete for market share at high prices, rather than to develop clinically superior medicines with public funding so that prices could be much lower and risks to companies lower as well.
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Introduction

In the undertaking of grand challenges and the search for vaccines and other magic bullets to eradicate diseases of the poor, the very high costs of pharmaceutical research appear everywhere. When companies like GlaxoSmithKline announce they will lower prices to a fraction of what they charge in affluent countries, the initial high price is justified based on the high risks and costs of research and development (R&D). For decades, the very high costs of R&D have been the industry's rationale for high prices in the developed world, and

the basis for claims that companies cannot afford research into primarily developing-world diseases, where high prices cannot be charged. The few companies that did not abandon vaccine R&D because prices were so low 'solved' that problem by charging 20–40 times more than they used to, citing the high cost of R&D. When Michael Kremer's version of an 'advance market commitment' (AMC) swept the policy world and was embraced by the G8 as a fiscal magic bullet that would result in new vaccines for malaria or AIDS, it was premised on meeting the allegedly high costs of R&D for multinational corporations, whose innovative researchers would find a vaccine for malaria or AIDS, where public or university researchers had failed (Kremer and Glennerster, 2004, pp. 10–11; Farlow, 2005).

Industry executives, well supplied with facts and figures by the industry's global press network, awe audiences with staggering figures for the cost of a single trial, like tribal chieftains and their scribes who recount the mythic costs of a great victory in a remote pass where no outside witnesses saw the battle. Companies tightly control access to verifiable facts about their risks and costs, allowing access only to supported economists at consulting firms and universities, who develop methods for showing how large costs and risks are; and then the public, politicians and journalists often take them at face value, accepting them as fact. The global press network never tells audiences about the detailed reconstruction of R&D costs for RotaTeq and Rotarix that found costs and risks were remarkably low up to the large final trials, and that concluded the companies recovered their investments within the first 18 months (Light *et al*, 2009). The companies could now sell these vaccines for rotavirus for one-tenth their Western price and still earn profits.

Pharmaceutical companies have a strong vested interest in maximizing figures for R&D and supporting centres or researchers who help them do so. Since the Kefauver hearings in 1959–1962, the industry's principal justification for its high prices on patented drugs has been the high cost of R&D, and it has sought further government protections from normal price competition. These include increasing patent terms and extending data exclusivity, without good evidence that these measures increase innovation (National Institute for Health Care Management, 2000; European Commission for Competition, 2008 (28 November); Adamini *et al*, 2009). Industry leaders and lobbyists routinely warn that lower prices will reduce funds for R&D and result in suffering and death that future medicines could reduce. Marcia Angell, the former editor of the *New England Journal of Medicine*, describes this as '… a kind of blackmail' (Angell, 2004, pp. 38–39). She quotes the president of the US industry's trade association as saying, 'Believe me, if we impose price controls on the pharmaceutical industry, and if you reduce the R&D that this industry is able to provide, it's going to harm my kids and it's going to harm those millions of other Americans who have life-threatening conditions'. Merrill Goozner, former chief economic correspondent for the *Chicago Tribune*, points out that no other research-oriented industry makes this kind of argument (Goozner, 2004). In fact, they do the opposite: when profits decline, they redouble their research efforts to find new products that will generate more profits. Not to do so guarantees their decline. The industry's view of European 'price controls' (actually, large-volume discounts) is that they do not allow recovery of huge R&D costs so that Europeans are 'free riders' on Americans and force US prices higher to pay for unrecovered costs the 'free riders' refuse to pay. This claim has been shown not to be supported by industry and government reports and to be illogical as well (Light and Lexchin, 2005).

The purpose of this report is to sharpen readers' critical skills in asking pointed questions about the seemingly insurmountable barriers of R&D, about the overpriced AMC that will result in most donations going to extra profits rather than more vaccinations (Light, 2007), and about how much global pharmaceutical companies can afford to discount (Plahte, 2005). By demythologizing in detail the most widely cited estimate of pharmaceutical R&D, the report will provide lessons in how such estimates are constructed. This exercise in critical sociology and economics builds on the substantial critiques of others (Public Citizen, 2001; Love, 2003; Angell, 2004; Goozner, 2004) but adds several new points. The report will conclude that the bigger problems lie elsewhere, with most R&D not being directed at discovering clinically superior medicines, even for affluent customers, because companies are so generously rewarded for developing hundreds of new products little better than the ones they replace. Policy needs to move away from decontextualized magic bullets and towards context-sensitive, socio-economic programmes of health in which medicines can play a critical role.

Industry Cost Estimates

The most widely cited figures (by government officials and the industry's trade association for its global news network) for the cost to discover and bring a new drug (defined as a 'new chemical entity' or 'new molecular entity'; not a reformulation or recombination of existing drugs) to market are US$802 million in 2000. This has been updated by 64 per cent to $1.32 billion in 2006 (PhRMA, 2009). If R&D costs increased another 64 per cent by 2012, the average cost would be $2.16 billion or approximately 2.7 times the $802 million estimate. These estimates are based on the study by Joseph DiMasi, Ronald Hansen, and Henry Grabowski done at the Tufts Center for the Study of Drug Development in Boston, Massachusetts (DiMasi *et al*, 2003a). This centre has received substantial industry funding for years and is a repository where companies submit their closely guarded figures on R&D. Only a few people, such as these health economists, are given access to the data. There is no more recent detailed study, and therefore this analysis will concentrate on it.

The 2003 study builds on more than a quarter-century of strategies to construct the wholly artificial 'fact' of average R&D costs per new drug, as the chief vehicle for generating political capital worth billions in tax concessions and price protection (Grabowski, 1976; Grabowski, 1978; Hansen, 1979; DiMasi *et al*, 1991). This long project in 'capitalized uncertainty' (McGoey, 2009) has exploited anxieties about the affordability of drugs with emphatic facts about how the great cost and risk of their development requires high prices. The Center was first founded at the University of Rochester with the backing of several large companies and then moved later to Tufts. The authors note that their previous (1991) study resulted in an R&D cost estimate more than double the estimate (in constant dollars) of Hansen's effort in 1979 (DiMasi *et al*, 2003a, pp. 153–158). They used a similar methodology in 2003 but with changes that have resulted in an estimate about three times greater than the 1991 study.

The $802 million cost explained

An overview of the $802 million study provides a helpful starting point. Essentially, the authors invited 24 US companies to participate in the new study of R&D costs, 12 accepted,

and 10 provided 'data through a confidential survey of their new drug R&D costs'. The investigators then turned to the Tufts Center database of compounds under investigation and drew a random sample of new drugs developed by the (self-selected) participating companies that were first tested in humans between 1983 and 1994 and were 'self-originated; that is, their development … was conducted under the auspices of the surveyed firm' (DiMasi *et al*, 2003a, p. 156). All but 8.9 per cent had been terminated (research abandoned) or approved by the US Food and Drug Administration (USFDA), by the cutoff date of March 2001.

The company R&D costs were broken down into expenditures on self-originated new chemicals; on new chemicals that had been developed elsewhere and licensed-in (rights purchased); and on variations of already-approved chemicals. The authors were interested in average costs per self-originated new chemical. The firms are not named but they accounted for 42 per cent of total industry R&D expenditures. The drugs are not named and no analysis was done by therapeutic class, even though R&D costs are known to vary widely across classes. (In classes like psychotropics, with many drugs, the small differences between new drugs and existing ones forces clinical trials to be large, in order to detect a small difference with statistical significance. Ironically, the smaller the therapeutic difference, the larger the costs of testing to gain approval.)

Based on the confidential, unverifiable data submitted by companies to the Tufts centre, the authors used their own complex, prior methods for estimating the attrition rate for Phase I, II and III trials. The reported trial sizes were larger than in the 1991 paper, averaging 5303 subjects. The company aggregate data on R&D costs were apportioned to the sample of compounds by phase, thus enabling the research team to estimate the cost per phase, corrected for what is usually called the 'failure rate', so that they could calculate the R&D costs per approved drug. No adjustment was made for taxpayer subsidies or tax deductions/credits specifically tied to R&D expenditures, which clearly reduce net R&D costs for a company. The mean cost was used even though the authors calculated that the median is 74 per cent of the mean (because a few very expensive drugs skew mean costs to the right). These methods enabled the authors to conclude that the 'average out-of-pocket cost per new [approved] drug is US$ 403 million (2000 dollars)' (p. 151).

Finally, the authors added the 'cost of capital', that is, the costs of returns from funds that would have been invested in the stock market, were the R&D project not undertaken. The authors used an estimated 'cost of capital' of 11 per cent, based on equity returns between 1985 and 2000, adjusted to remove inflation (implicitly assuming that similar returns could be obtained, risk-free, in the future). They compounded the 11 per cent over the estimated time (90.3 months) required for clinical trials and USFDA review; although it is unclear just how the times were estimated. Compounding at 11 per cent doubled the estimated cost for R&D from $403 million to 'a total pre-approval cost estimate of US$802 million (2000 dollars)' (p. 151).

Critiquing the $802 Million Cost Estimate

Problems with the sampling and data

DiMasi *et al* do not explain which 24 firms were invited to participate or why, and little is said about which 10 finally took the trouble to provide the data. Given the centrality of the

issue and the prominence of the Center, it is puzzling that more than half of those invited did not participate. Because the participating companies were not randomly selected, taking a random sample of their self-originated new molecules does not make the final sample random. In addition, that sample is based on closely held information submitted by self-selected companies to the Tufts Center on their R&D activities and their costs. Which drugs were regarded as 'self-originated' becomes less clear the closer one looks. The investigators characterized them as 'conducted under the auspices of the surveyed firm' but have a footnote that opens the door to a company developing 'self-originated' drugs with NIH or other government agencies, universities or other firms (DiMasi *et al*, 2003a, p. 156). The sample (of firms) could be skewed toward those with higher R&D costs. The sample of drugs may be skewed as well; drug names were not disclosed, and therefore one cannot tell how many were among the 60 per cent of new chemical entities (NCEs) that the USFDA regards as warranting no 'priority' status for not providing therapeutic advances. For these and related reasons, studies and figures like these should be greeted with scepticism about their validity and with calls for greater transparency, given that companies try to use high R&D costs to justify high prices. Instead, their figures are accepted with awe.

The authors do not mention any efforts to verify the costs reported by the companies or clean the data. One does not know how companies calculated their R&D costs or what they included. Methods of identifying and counting R&D costs may change with changes in company administrations and after mergers or acquisitions. Large costs might be included as part of a company's overall R&D strategy, that are not directly related to discovering and developing new molecules. The Canadian Patented Medicine Prices Review Board (2002), for example, reported that companies include in R&D all the costs of their contracting related to R&D, for example with biotech companies, contract research organizations and other organizations; the cost of land and buildings used substantially but not exclusively for research or development; and general administrative overhead and major equipment. Other costs mentioned in the R&D literature that some companies may include in their total R&D costs are large legal expenses for developing patents and other IP protections and legal defence against challenges; large fees paid to doctors to participate in clinical trials and become key opinion leaders, to promote new drugs; the costs of ghost managing and authoring research results, as well as support for medical journals publishing them; executive costs in finding and negotiating with other firms for new products; lectures and courses to inform physicians about current research; or company-wide technical upgrades, like software or computers (US Office of Technology Assessment, 1993; Barton and Emanuel, 2005).

A final sampling problem is that, according to an unpublished appendix by the authors, R&D costs for self-originated NCEs are 4.4 times higher than for licensed-in NCEs, and R&D costs for licensed-in NCEs are 3.4 times higher than for non-NCE variations on existing drug products (DiMasi *et al*, 2003b). Thus their estimate of NCE R&D costs is far higher than the average cost per newly approved drug product. From 1990 to 2000, only 35 per cent of new drug products were NCEs (US Food and Drug Administration, 2004). Even fewer were developed in-house: 62.4 per cent of the companies approved NCEs, according to the authors, or 22 per cent of all new drug products. There is reason to believe this figure is still lower because of well-documented examples when companies have claimed that they researched and developed a drug themselves, but independent evidence indicated they

did not (Mitsuya *et al*, 1989; General Accounting Office, 2003). Yet from the moment in December 2001 when the results of this 2003 DiMasi *et al* study (2003a) were presented to the world press by the president of Merck – over a year before its journal publication – the $802 million figure has erroneously been characterized as the R&D cost 'per new drug', not the costliest one-fifth (Harris, 2001). The global press network of Merck and the industry trade association, PhRMA (Pharmaceutical Research and Manufacturers of America), made this the official new 'fact' used in all press material. For some reason, the *Journal of Health Economics* did not consider this as pre-publication, and their publishing it more than a year after the press conference turned a press 'fact' into a legitimate, scientific fact (Love, 2003).

Costs of discovery unknown and highly variable

Neither the 2003 DiMasi study (2003a) nor any others includes cost figures for basic research to discover new medicines – the key to research for neglected or any other diseases. There are good reasons why. Discovery can range from 3 months to 30 years (Goozner, 2004). Many major discoveries (such as penicillin) have occurred by accident, by noticing some peculiar reaction while investigating something else (Le Fanu, 1999). Others have taken decades of frustrating research, usually funded by non-corporate sources. From a methodological point of view, basic research often contributes to several drug discoveries later. It is also unclear how far back one should go to count up the costs of discovery, given that often there are several strands of research that are pieced together. In Angell's view, the critical step in 'discovering' a new drug is understanding how the disease works and finding one or two good targets of vulnerability in the defences of a disease for intervention. Basic research 'is almost always carried out at universities or government research labs, either in this country or abroad' (Angell, 2004, p. 23). Companies under pressure from quarterly reports have difficulty justifying long searches for breakthrough drugs to investors.

Goozner documents in detail how most of the science for many recent 'breakthrough' drugs, and many of the essential techniques for doing the research and manufacturing, were funded by taxpayers through federal agencies. In the long, difficult search for effective drugs to treat AIDS, Goozner assembles evidence that the key companies spent $150–$200 million each, for an industry total of $2 billion, while the US government spent close to $10 billion (Goozner, 2004, pp. 157–163). Goozner estimates that all AIDS R&D costs from the beginning were earned back in one year. But he also found that as revenues soared on high prices, so did company claims of how much R&D cost them.

Little company R&D is devoted to basic research. Although industry association reports, based on unverified numbers from its members, claim that companies invest on average 17–19 per cent of sales in R&D, the most authoritative data come from the long-standing survey by the US National Science Foundation (2003). Its data document that pharmaceutical firms invest 12.4 per cent of gross domestic sales on R&D. Of this, 18 per cent, or 2.4 per cent of sales, went to basic research. More detailed reports from the industry indicate the percentage of R&D going to basic research is even smaller, about 9.3 per cent (or 1.2 per cent of sales) (Light, 2006). Thus the net corporate investment in research to discover important new drugs is about 1.2 per cent of sales, not 17–19 per cent. Most pharmaceutical R&D (11.2 per cent of sales) is spent on new drugs of little therapeutic

benefit rather than for breakthrough drugs, even in countries with price boards (Morgan *et al*, 2005). From a drug company's point of view, it makes sense to focus most research on extending or replacing existing best-selling drugs, in order to obtain government protection from generic price competition.

In the $802 million estimate, DiMasi *et al* (2003a, p. 166) 'solve' the problems of no data on the costs of discovery by estimating an average cost of $121 million and adding it in at the beginning of their R&D estimate. This added 52.0 months as 'the average time from synthesis of a compound to initial human testing for self-originated drugs …' When compounded by the 'cost of capital' this accounts for more than one-third of the $802 million estimate, a large number that seems unwarranted for several reasons. First, there is no verifiable cost estimate. Second, costs vary greatly. Third, when PhRMA provided detailed breakdowns of R&D costs, only about a third of all preclinical costs appeared to involve basic research for discovery (Pharmaceutical Research and Manufacturers of America, 2002). Finally, 84.2 per cent of all funds for discovering new medicines come from public sources (Light, 2006). Therefore, a more realistic conclusion is that the costs of R(research) are unknown and highly variable.

Tax savings are real and substantial

The authors argue that special tax provisions for R&D should not be considered tax breaks, and that the gross costs of R&D should not be reduced by tax savings. That might be reasonable if R&D were treated like other long-term investments, and depreciated gradually over time, but R&D costs come from gross profits and create a 100 per cent immediate deduction from taxable profits. As the comprehensive review by the OTA stated, 'The net cost of every dollar spent on research must be reduced by the amount of tax avoided by that expenditure' (US Office of Technology Assessment, 1993, p. 15). When the top marginal tax rate was 46 per cent, the OTA conducted the most comprehensive review of pharmaceutical research costs and estimated that tax savings and credits reduced net costs by nearly 50 per cent. The top marginal tax rate is now 35 per cent, and the average tax savings for the DiMasi study period (2003a) is about 39 per cent (Tax Policy Center, 2002).

However, tax savings from R&D are even higher than the 35 per cent top rate, because of additional special credits including an extra 20 per cent R&D tax credit on expenditures above a specified base amount, and special tax credits for manufacturing plants in selected tax havens. The OTA reported that the latter were worth more than 14 times basic R&D tax credits. Estimating overall tax savings is also made nearly impossible because companies keep figures secret. But one can get a rough idea from the 'tax holiday' that Congress offered in 2005 to allow US companies to 'repatriate' sheltered foreign profits at a 5.25 per cent tax rate. Using a corporate tax rate of 35 per cent, companies would save up to 29.75 per cent on profits in locations with no taxes (for example, Puerto Rico, for many years) and less in locations with a small tax (Andrews, 2005 (1 February); Berenson, 2005 (8 May)). Pfizer had accumulated untaxed foreign profits of $38 billion, Merck $18 billion, Johnson and Johnson $14.8 billion, and Eli Lily $9.5 billion, generated through strategies such as manufacturing drugs in tax havens and buying them back at high prices so most of the profits accrued in the havens. If these four firms alone saved $24 billion (29.75 per cent of $80 million), how much were overall industry R&D costs reduced by the combination of low tax-haven taxes, and tax holidays? No one knows, but it is considerable.

A reasonable guess is that half of corporate R&D expenses are paid for by taxpayers over the long term.

Half of 'costs' are profits foregone

Half of the authors' estimated R&D costs consist of the 'cost of capital', based on an estimated 11 per cent return on funds invested, had R&D projects not been undertaken. This is a common method that firms use to decide whether or not they should build a new hotel or research a new drug. They estimate how much they hope to make by investing their capital in a new hotel or drug compared to how much they would make if they put their capital into a generic investment like an equity or bond fund. If projected sales and profits do not exceed the estimated cost of capital (the foregone investment returns), they drop the project. Few experts note, however, the profound change when the estimates from this exercise are relabelled as 'costs' that insurers and governments should repay; particularly in light of recent stock market losses, which make clear that equity investment returns are far from risk-free.

In other industries, huge investments to develop new products, like a new chip from Intel, do not lead firms to make the argument for government-protected prices by claiming that 'You owe us for all our R&D costs, plus what we would have made had we not undertaken the project in the first place'. Thus estimated high profits get transposed into costs. Calculating the cost of capital is a widely accepted exercise to determine whether a project should be undertaken; but as a claim on public money or citizens' cash, it is unreasonable. Further, experts argue that innovative companies must do R&D, and this is a regular cost of doing business; so estimated profits foregone should not be added to out-of-pocket costs at all (Engelberg, 1982). If revenues are coming in from other products, then the costs are recovered as one goes along. Even if one were to accept the argument that profits foregone should be included as a 'cost', US government guidelines call for using 3 per cent, not the 11 per cent used by DiMasi and colleagues (United States Office of Management and Budget, 2003).

A final basic point is that the industry and researchers cannot have it both ways. They cannot treat R&D costs as if they are a long-term capital investment when tax authorities do the industry the favour of treating them as an ordinary business expense, fully deductible each year. This point does not imply that research should not lead to patents or other IP protections, nor that there are no long-term benefits; but financially R&D is an ordinary business expense, not a capital cost. Using 'cost of capital' to double an artificially constructed cost of R&D per drug is one of several ways that economists have developed since the 1970s to inflate estimates (Wardell and Lasagna, 1975; Grabowski, 1976; Hansen, 1979). If companies and researchers really believe the cost of capital argument, then they should apply to tax authorities for R&D expenses to be amortized over a 10–20-year period and no longer deducted from taxable profits each year.

Trial costs inflated

External evidence leads one to question the costs per trial used in the $802 million estimate. First, an October 2001 study by the US FDA found that the clinical trials for 185 new molecules tested between 1995 and 1999 averaged 2667 subjects (Love, 2003, p. 9). The DiMasi team used an average of 5303 subjects, or about twice as many (DiMasi *et al*, 2003a,

p. 177). Second, the full cost of each trial phase was used by the DiMasi team to estimate the cost of each compound terminated; yet companies often withdraw drugs part way through a trial in order to avoid its full expenses. Third, the DiMasi team refers rather opaquely to a complicated set of steps taken to arrive at the mean cost per trial and per subject. The resulting figure of $23 572 per subject is six times the average cost per subject of $3861 reported by the National Institutes of Health for 1993, at the costly (later) end of the DiMasi period (1983 to 1994) (Love, 2003, pp. 10–11).

Exaggerated time for R&D

The $802 million estimate is based on 52 months for preclinical research, 72 months for trials and 18 months for regulatory review, a total of 142 months or 11.8 years (DiMasi *et al*, 2003a, pp. 164–166). Maximizing the length of time not only dramatizes how long and hard companies work to discover and develop a new medicine, but also maximizes the multiplication of profits foregone. Long development times are a major reason given for needing high prices. These figures, however, do not square with the lengths for trials actually reported by companies to the US FDA in the Federal Register. Trial length declined from almost 8 years for trials started in 1985 to less than 3 years for trials started in 1995 (Keyhani *et al*, 2006). Regulatory review times dropped from 2½ years to less than a year. Thus, for medicines that started testing in 1995, total trial and review time was down to less than 4 years in the United States and even less in Europe (plus the unknown time for preclinical research discussed above). The Keyhani study also documents that 'development times are not a factor in rising drugs prices' (Keyhani *et al*, 2006, p. 467). The shortest trial times were for AIDS and cancer drugs, which also received the greatest external funding for R&D. If recovering the *net corporate* costs of R&D is the principal reason for high prices, then the prices of new cancer and AIDS drugs should be low.

Corporate R&D risk much lower too

Reports by industry routinely claim that companies must test 5000–10 000 compounds to discover one drug that eventually comes to market (EFPIA, 2010, p. 7). Marcia Angell (2004) points out that these figures are mythic: they could say 20 000 and it would not matter much, because the initial, high-speed computer screenings consume a small per cent of R&D costs (Boston Consulting Group, 2001). Short lists of likely candidates are further tested and developed, also for a relatively small percentage of total R&D cost, resulting in a small number of candidates that seem both effective and safe enough to develop into final products. The DiMasi team calculated that 21.5 per cent (about one in five) of drugs entering human clinical trials receive US FDA approval (DiMasi *et al*, 2003a). Most of the trial costs are incurred in Phase III trials, when the risk of withdrawal is low, less than one in two. Thus company risk drops precipitously as research costs rise.

Many products that 'fail' would be more accurately described as 'withdrawn', usually because trial results are mixed; or because a company estimates the drug will not meet their high sales threshold for sufficient profitability. The difference between 'failure' and 'withdrawal' is important, because many observers suspect that companies withdraw or abandon therapeutically beneficial drugs for commercial reasons. Such withdrawals by companies, whether for commercial or clinical reasons, appear to have increased over time

(Waxman *et al*, 2006). On the other hand, some drugs with known risks of toxic reactions are not withdrawn but further tested, approved and used (Olson, 2004; Carpenter *et al*, 2008; Light, 2010).

Company financial risk is not only much lower than usually conveyed by the '1 in 5000' rhetoric, but companies spread their risk over a number of projects. The larger companies are, and the more they merge with or buy up other companies, the less risk they bear for any one R&D project. The corporate risk of R&D for companies like Pfizer or GlaxoSmith Kline are thus lower than for companies like Intel that have only a few innovations on which sales rely.

Measuring 'average' costs – median costs much lower than mean

Finally, calculations of costs or trial sizes or lengths of development should be done using medians, not means, because it is well known that a few outliers can pull up the mean by being notably more costly, large or long. For example, the R&D costs of the vaccines Rotateq and Rotarix were greatly increased because Phase III trials had to be 10 times larger than usual (Light *et al*, 2009). The DiMasi team reports that median trial costs were 74 per cent of mean trial costs (DiMasi *et al*, 2003a, p. 162), so that the $802 million figure would have been reduced to $593 million had median costs been used. Using the mean is just one more way that the DiMasi estimates overstate drug development costs (Light *et al*, 2009).

Making a More Realistic Estimate of R&D Costs

A more realistic estimate is hampered by lack of access to the uncleaned, unverified data used for the $802 million and related estimates; but some original and informative calculations can be made. In the first column of Table 1 are reproduced the cost estimates of the DHG 2003 study (DiMasi *et al*, 2003a). These estimates are corrected in column 2 for taxpayer subsidies (at 50 per cent). This reduces the cost per 'self-originated' NCE from $403 million to $201 million. Using DHG's calculation that the median is on average 74 per cent of the mean, the more accurate median development cost is $149 million (column 3).

If 'cost of capital' is to be included, it should be done responsibly, according to well-established guidelines. The DiMasi team used a rate of return (11 per cent compounded annually), which is much higher than the 3 per cent called for by US government guidelines (United States Office of Management and Budget, 2003) and the US Panel on Cost-Effectiveness in Health and Medicine (Russell *et al*, 1996; Weinstein *et al*, 1996). Canadian guidelines call for a 5 per cent rate (Canadian Coordinating Office for Health Technology Assessment, 1997). We use both in our calculations as well as a 7 per cent discount rate in order to provide low, medium and high estimates. These capitalized costs accept the development times of DiMasi *et al*, which (as discussed above) may be overstated. The resulting cost-range in the second half of Table 1 is $180-$231 million *median* cost per approved, self-originated NCE.

The R&D cost of the 'average new drug', however, is considerably lower than the most costly one-fifth (self-originated NCEs). Table 2 applies the cost ratios from DiMasi (DiMasi *et al*, 2003b) to the proportion of new drugs that are self-originated, licensed in, or based on existing molecules, to arrive at the mean and median development costs for all new drugs.

Table 1: Revised cost estimates, self-originated new chemical entities (million US$, year 2000)

Phase	*DHG 2003 gross costs per approved drug*	*Net mean costs per approved drug (-50% tax savings)*	*Net median costs per approved drug (-50% tax savings)*	*Capitalization factors for different discount rates*			*Net median capitalized cost per approved drug*		
				High (7%)	*Medium (5%)*	*Low (3%)*	*High*	*Medium*	*Low*
Phase I	70.7	35.3	26.2	1.57	1.39	1.22	41.1	36.2	31.9
Phase II	77.6	38.8	28.7	1.45	1.31	1.18	41.6	37.5	33.7
Phase III	126.0	63.0	46.6	1.23	1.16	1.10	57.5	54.2	51.1
Animal	7.6	3.8	2.8	1.48	1.33	1.19	4.2	3.7	3.3
Trial total	281.9	141.0	104.3	1.38	1.26	1.15	144.3	131.7	120.1
Preclinical	120.8	60.4	44.7	1.94	1.61	1.33	86.5	72.0	59.7
Total	402.8	201.4	149.0	1.55	1.37	1.21	230.9	203.7	179.7

Table 2: Net cost per average approved drug, survey firms (million US$, year 2000)

Description	*% of approved drugs*	*% of R&D costs*	*Net mean clinical cost per 100 approved drugs*[a]	*Net median clinical cost per 100 approved drugs*[a]	*Net mean clinical cost per approved drug*[a]	*Net median clinical cost per approved drug*[a]
Self-originated NCEs	21.8	74.9	6011	4448[b]	275.2	203.7[c]
Licensed-in NCEs	13.2	10.2	819	606[d]	62.2	46.0[e]
Existing-molecule drugs	65.0	14.9	1196	885[d]	18.4	13.6[e]
Total	100.0	100.0	8025	5939[f]	80.3	59.4[g]
Self-orig ratio to licensed-in	—	—	—	—	4.4	4.4[h]
Self-orig ratio to existing	—	—	—	—	15.0	15.0
Licensed-in ratio to existing	—	—	—	—	3.4	3.4

[a]Reduced by 50 per cent tax savings; cost of capital added at 5 per cent (multiplies raw costs by 1.37; see Table 1).
[b]Net mean or median clinical cost per approved self-originated NCE from Table 1, multiplied by 21.8 (the number of self-originated NCEs in 100 approved drugs).
[c]Mean calculated using costs and capitalization factors from Table 1 (result not shown in table); median from Table 1.
[d]Calculated based on known share in total costs; 10.2 per cent for licensed-in NCEs, 14.9 per cent for existing-molecule drugs (DiMasi *et al*, 2003b, p. 2).
[e]Calculated by dividing cost per 100 approved drugs for licensed-in NCEs or existing-molecule drugs by the number of each (13.2 and 65, respectively).
[f]Calculated from self-originated NCE costs, stated to be 74.9 per cent of total R&D costs (DiMasi *et al*, 2003b, p. 2).
[g]Average cost for all types of drugs; calculated by dividing total cost per 100 approved drugs by 100.
[h]Based on our calculations; matches the ratios in DiMasi *et al* (2003b, p. 3, note 1).

Table 3: Most new drugs and new indications for older drugs do not represent any significant therapeutic advantage – 1996–2006

Category	*Number*	*Per cent*
Major therapeutic innovation in an area where previously no treatment was available	2	0.2
Important therapeutic innovation but has limitations	38	3.9
Some value but does not fundamentally change the present therapeutic practice	106	10.8
Minimal additional value and should not change prescribing habits except in rare circumstances	251	25.5
May be new molecule but is superfluous because does not add to clinical possibilities offered by previously available products	442	45.0
Without evident benefit but with potential or real disadvantages	77	7.8
Decision postponed until better data and more thorough evaluation	67	6.8
Total	983	100.0

A look back at pharmaceuticals in 2006: Aggressive advertising cannot hide the absence of therapeutic advances (Prescrire International 2007; 16: 80–86).

In column 1 of Table 2 is listed the proportion of new drugs that are self-originated NCEs (21.8 per cent), licensed-in NCEs (13.2 per cent) and other new drugs (65.0 per cent). Based on the DiMasi *et al* data (column 2), 74.9 per cent of all company R&D was spent on self-originated NCEs, 10.2 per cent on other NCEs and 14.9 per cent on variations of existing molecules that make up all the remaining new drugs approved (DiMasi *et al*, 2003b). Marcia Angell questions whether this can be true, and good data would help. But let us see what the net mean and median R&D cost is using the authors' proportions. Columns 3 and 4 are transitional or calculation columns in which we calculate the net mean and median cost per 100 average approved drugs.[1]

The overall mean and median net corporate R&D costs (columns 5 and 6) were $80.3 million and $59.4 million, respectively. Had we used estimates without the cost of capital, the figures would be $58.7 million and $43.4 million (based on the 1.37 increase in cost at 5 per cent, shown in Table 1). Such low estimates seem unbelievable until one learns that the audited costs of all clinical trials submitted by pharmaceutical companies in the late 1990s to the Internal Revenue Service averaged only $22.5 million (Love, 2003, pp. 7–8). Our higher figure may be due to some of the over-estimates we described above (and cannot adjust for),

1 To do this, we first calculate costs for self-originated NCEs by multiplying $275.2 (the mean cost from Table 1, capitalized at 5 per cent as was done for median costs; capitalized mean amounts not shown in Table 1) and $203.7 million (the median cost from Table 1, capitalized at 5 per cent) by 21.8 (the number of self-originated NCEs in 100 newly approved drugs; $\$275.229 \times 21.84 = \$6011$ shows the exact, not rounded, numbers). We then divide the results ($6.0 billion and 4.4 billion, respectively) by 0.749 to determine total mean and median costs for all types of drugs, and enter the results on the total line. Finally, we multiply these totals by the appropriate cost shares for licensed-in NCEs and existing-molecule drugs (10.2 and 14.9 per cent, respectively), to determine their mean and median costs in a cohort of 100 approved drugs.

The final step is to use the cost for our cohort of 100 approved drugs to calculate costs for one licensed-in NCE or existing-molecule drugs, and an overall average for all types of new drugs. For mean costs for licensed-in NCEs, for example, we divide the $819 million total by 13.2 (the number of these drugs in our cohort). The same calculation is done for median costs, and for existing-molecule drugs; the totals are determined by adding up mean and median costs for all three types of new drugs.

such as the possibly biased firm sample, R&D costs being 'padded' with legal and other non-research costs, poorly documented preclinical costs, overestimated trial costs and sizes, overly long trial phase lengths, and exaggerated risks of failure. But when thinking of an average newly approved pharmaceutical, these costs are much more representative than the $802 billion commonly cited by industry.

The larger point is that, based on independent sources and reasonable arguments, one can conclude that R&D costs companies a median of $43.4 million per new drug, just as company supported analysts can conclude they are over 18 times larger, or $802 million. Readers should appreciate the constructed nature of R&D cost estimates and *always* ask very closely about where the data for an estimate come from, how they were assembled and whether they can be verified.

Conclusion

The high prices of new medicines, the discounts offered to poorer countries and the new policy tools like the overpriced AMC are built on the mythic costs of R&D and their mythic promise to save millions more lives than they can (see Light, 2009, pp. 14–17). The AMC is structured as a surplus contract and does not even try to fulfil its original intent of rewarding the discovery of new vaccines for the poor (Light, 2009). It prices extra doses well above what low-income countries can afford, and also above the cost of manufacturing. GAVI, the Global Alliance for Vaccines and Immunization, has embraced the AMC, with hopes that it will save 10 times more children than it realistically can (Light, 2009); and has created for itself a long-term financial burden that transfers donations into profits on blockbuster pneumococcal conjugate vaccines, throwing itself into a financial crisis (Butler, 2010). GAVI has taken $1.3 billion from its core funding for much more cost-effective programmes to supplement the $1.5 billion donated for the AMC, but this is not nearly enough to fund the patent-preserving deep discount strategy of the AMC for purchasing vaccines. In the meantime, the heavily promoted AMC is poised to disrupt the delicate ecology in which neglected disease research actually takes place (Moran, 2005; Pharmaceutical R&D Policy Project, 2005). The self-perpetuating high-cost myth also produces wasteful and inefficient corporate research structures (Fisher, 2009) because companies do not think lean, though they talk of nothing but lean thinking. In fact, no one wants to believe that R&D costs might be much lower than claimed, or look more deeply into them with adequately funded studies, because so many people benefit from the high-cost myths and the generous budgets supporting them. Nevertheless, this article provides reason for policy makers and developers to lower their estimates of how risky and expensive R&D must be to develop medicines for global health problems (Pharmaceutical R&D Policy Project, 2005; Moran *et al*, 2007).

The deeper problem is that current incentives reward companies for developing mainly new medicines of little advantage, and then competing for market share at high prices; rather than rewarding development of clinically superior medicines with public funding, so that prices could be much lower (Light, 2010). One or two out of every 20 newly approved medicines offer real advances, and over time they have accumulated into a highly beneficial medicine chest for humanity (see Table 3). Approving new medicines using non-inferiority or superiority trials against a placebo, and using substitute or surrogate end points, has resulted

for years in about 85 per cent of new drugs being little or no better than existing ones (Light, 2010). These then become the medicines the rest of the world wants, because the rich have them and presumably benefit from them. But in fact, they have spawned an epidemic of serious adverse reactions that rank behind stroke as a leading cause of death and cause about 4.4 million avoidable hospitalizations worldwide (Light, 2010). Thus the mythic costs of R&D are but one part of a larger, dysfunctional system that supports a wealthy, high-tech industry, gives us mostly new medicines with few or no advantages (and serious adverse reactions that have become a leading cause of hospitalization and death), and then persuades doctors that we need these new medicines. It compromises science in the process, and consumes a growing proportion of our money. Many recent developments are addressing parts of the ways in which Western medicines are developed, tested and marketed, but in the meantime, a new generation of Indian and Chinese executives see how vulnerable the dysfunctional Western practices are (Frew *et al*, 2008).

About the Authors

Donald Light is Lokey visiting professor at Stanford University and a professor of comparative health-care at the University of Medicine and Dentistry of New Jersey. He is an economic and organizational sociologist who studies health care systems and pharmaceutical policy. As a founding fellow of the Center for Bioethics, he has become concerned about exaggerated claims of risk, cost, and benefit of new medicines that result in misguided policies. Professor Light is co-author and editor of The Risks of Prescription Drugs (2010). His research has appeared in leading medical and social science journals.

Rebecca Warburton is an associate professor and a health economist, specializing in the cost-benefit analysis of health-related public projects. Her current research primarily concerns assessing the validity of industry-sponsored estimates of the cost of drug development, and assessing the costs and effects of patient safety improvements. She has a PhD in economics from the University of London (1995), and an M.Sc. in economics from the London School of Economics (1980). Before coming to the University of Victoria in 1998, she worked for 10 years as a policy analyst and program evaluator for the British Columbia Ministry of Health.

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