ASSESSING CLAIMS ABOUT THE COST OF NEW DRUG DEVELOPMENT: A CRITIQUE OF THE PUBLIC CITIZEN AND TB ALLIANCE REPORTS

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EXECUTIVE SUMMARY

A number of critics of the pharmaceutical industry have maintained that new drug development costs are substantially lower than are estimates that we have published. They have relied generally on two reports for alternative estimates of the average cost of new drug development. One was a report published by the advocacy group Public Citizen on its Web site in 2001. The other was a report prepared to examine the financial viability of developing a new drug for a tuberculosis indication (Global Alliance on Tuberculosis Drug Development report on the economics of TB drug development [TB Alliance]). We carefully examined the methodologies and data used in both reports. In the case of the Public Citizen report, fundamental economic principles were ignored and published data were utilized improperly in ways that bias their numbers downward substantially. The report on TB drug development projects costs that the authors never intended to be used as representative of drug development as a whole. There are a number of reasons why these projections should not be compared to our results. Our key findings are as follows:

- Pharmaceutical R&D is an investment with expenditures made years before any potential returns are earned. Based on standard principles in economics and finance, these investments have opportunity costs that are real and highly relevant. The time costs associated with new drug development are inappropriately ignored in their entirety in the Public Citizen report.

- The Public Citizen report, noting that R&D expenditures are deductible under the corporate income tax, maintains that R&D cost estimates should be reduced in percentage terms according to the corporate income tax rate. The estimates in our studies were meant to examine trends in private sector resource costs, and changing tax structures mean that after-tax costs can mask such trends. The Public Citizen perspective, however, also reflects a fundamental misunderstanding of the nature of the corporate income tax. Profits (i.e., net income) are the target of the tax, not gross income. Deducting business costs is just the mechanism by which the targeted tax base (profits) is determined.

- Public Citizen used published annual data on industry R&D expenditures from the industry's U.S. trade association and FDA data on the number of new drug application (NDA) approvals to measure pre-tax out-of-pocket R&D costs. However, they used incomplete and mismatched data to derive the ratios that resulted in their cost estimates. The numerators of their ratios exclude much relevant expenditure and the denominators are inflated by including approvals of firms that did not contribute expenditure data to their numerators. For these reasons, their estimates using published data are deeply flawed and substantially understate R&D costs.

- Public Citizen also used the NDA as its unit of observation, as opposed to a new drug (i.e., a new active ingredient). This is both technically and conceptually inappropriate. Many of the NDA approvals are not for new molecular entities (NMEs). However, many of these approvals are also not for new product presentations and/or are obtained by firms that have no relationship with respect to the drug in question to the sponsor of the original NME approval. On a conceptual level, the costs of obtaining non-NME NDA approvals on line extensions are

intimately related to the costs of the associated NME NDA approvals. The most appropriate perspective to take on the R&D process is to use a new drug (active ingredient) as the unit of observation and examine costs over the lifecycle of the drug.

- The TB Alliance report estimates are projections for what is really a special case. The estimates were based on assumptions about developing a drug for a tuberculosis indication that were modeled after the development of an antibiotic orphan drug that was given accelerated approval status by the FDA. While this may be reasonable for modeling a drug to treat a tuberculosis indication, it is not representative of drug development as a whole. Development costs for such indications would typically be well below average.

- The development program in the TB Alliance report also assumed a single pivotal trial. While it is possible to succeed in this way for a tuberculosis indication, it has been very uncommon for the FDA to accept just a single pivotal trial.

- The TB Alliance report projects costs for a single indication. Our R&D cost estimates are costs per approved drug, not costs per approved indication. Many drugs are investigated for multiple indications prior to their first marketing approval. This can help explain why the number of subjects posited in the TB Alliance report is only one-quarter the average number of subjects in NDAs for NMEs found by independent analysis.

In a series of studies on the economics of new drug development covering

pharmaceutical R&D over the last forty years (DiMasi et al., 2003 [hereafter DHG]; DiMasi et

al., 1991 [hereafter DHGL]; Hansen, 1979), we have examined trends in private sector average

resource costs of developing new drugs from invention to regulatory marketing approval. In

recent years, advocacy groups and other critics of the pharmaceutical industry have used certain

reports to suggest that pharmaceutical R&D costs are really much lower than the estimates that

we have obtained. In particular, one or both of two reports (Public Citizen, 2001; Global

Alliance on Tuberculosis Drug Development, 2001 [hereafter TB Alliance]) have been cited to

dispute our results (e.g., Relman and Angell, 2002; Goozner, 2004; Angell, 2004). These reports

have not undergone anonymous peer review, and have not otherwise been scrutinized fully for

methodological flaws or the propriety of using results from them as comparators to our work.[1]

This report provides comprehensive critiques of the methods used in the two reports and

examines the appropriateness of using the results obtained as alternatives to the estimates in our

most recent R&D cost study (DHG).

1. Public Citizen Report

Public Citizen (2001) issued a report on its Web site in July 2001 that purported to show

that pharmaceutical industry R&D costs are much lower than what the industry had claimed.

They took two basic approaches to challenging a figure that industry had been using (an

extrapolation of our 1991 study estimate). The first approach simply consisted of ignoring the

time costs of new drug development (described as "theoretical", and so presumably not real) and

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[1] Dickson and Gagnon (2004) and Ernst & Young (2001) provide partial discussions of the cost analyses in Public Citizen (2001).

then reducing the out-of-pocket cost from our previous study according to a statutory corporate income tax rate.[2]

1.1 Opportunity costs

Our studies report both out-of-pocket and capitalized costs. The relevance and validity of including capitalized cost values is not in question in economic and finance. These are real, not "theoretical," costs. They are especially relevant for investments in pharmaceutical R&D since the development cycles are so lengthy, resulting in long periods between when investment expenditures are made and the potential returns are earned. In essence, capitalized cost estimations include a monetary value of the time costs associated with development.

For example, suppose that two investment projects, A and B, yield the same stream of net returns and that the out-of-pocket costs associated with these investments are identical. However, investors realize the returns from project A immediately, while investors must wait 10 years before they earn any returns from project B. Rational investors will perceive that the real cost of project B is much higher than the cost of project A.[3]

To put the issue in somewhat different terms, suppose that the stream of net returns after marketing begins is identical for two investments. However, one of the investment projects costs $400 million out-of-pocket spent over 12 years before any returns are realized. The second investment project costs $500 million out-of-pocket, but it is spent over 9 years before its returns are realized. How do we assess which investment is better? The net return distributions are the same, but there is no way of knowing which investment is superior just from the difference in out-of-pocket cost. The projects, however, can be meaningfully compared if time costs for the

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[2] Public Citizen later applied the same approach to the out-of-pocket cost in DHG and posted the result on its Web site. It is worth noting that acceptance of their no-opportunity cost/tax-adjusted figure is an implicit endorsement of the validity of our underlying data.
[3] This example was taken from DiMasi (2002).

two investments are determined and added to the out-of-pocket costs to yield a single monetary measure of total cost.

Public Citizen did not offer a justification in its report for why time costs do not exist or should be ignored,[4] but some supporters of their report have tried to rationalize their position. Relman and Angell (2002) and Angell (2004) offer a rationale that is really a non sequitur. They assert that there are no opportunity costs to pharmaceutical R&D because pharmaceutical firms "have no choice but to spend money on R&D if they wish to be in the pharmaceutical business" (Angell, 2004, p.45). Of course, one could literally say this about any industry, but it has no relevance to whether there are opportunity costs for industrial pharmaceutical R&D.

An investment is the expenditure of funds today with the hope of earning a return on those expenditures in the future. Clearly pharmaceutical R&D meets that definition. As argued above, it is also the case that the longer the period between when the investment expenditures are made and when returns are earned, the higher are the full economic costs associated with the investment. In contravention with basic economic principles, Angell (2004, p.45) also asserted with regard to pharmaceutical firms, "They are not investment houses. So you can hardly look at the money spent on R&D as money that could have been spent on something else." Of course, if conditions warrant, firms can indeed reduce the amount spent on pharmaceutical R&D and increase their spending on other lines of business, develop new lines of business, or return more

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[4] However, in an interview with the media upon the release of the report, the director of the section of Public Citizen that issued the report, Frank Clemente, offered an analogy to purportedly debunk the opportunity cost notion. He stated, "That's crazy,…It's the equivalent of saying that if I were to pay $20,000 in cash for a new car, it would actually cost more than $40,000 because the $20,000 could have been invested in the stock market." (Bayout, 2001). This is a false analogy. In this context an appropriate, albeit unrealistic, analogy would be a situation in which a consumer faces a choice between purchasing two different automobiles for which the consumer is indifferent with regard to their physical attributes. Suppose that the price of each vehicle is $20,000 that must be paid in cash now. However, suppose also that vehicle A is available immediately to the consumer, but the dealer prep time on vehicle B is 10 years. Any rational consumer would, at least intuitively, consider the effective cost of vehicle B to be much higher than cost of vehicle A.

of their current profits to shareholders in the form of increased dividend payments (thereby, letting the owners of the firm use these funds for purposes that are more valuable to them).

A logical implication of the Public Citizen/Relman/Angell perspective on economic reality is that pharmaceutical firms must routinely breach their fiduciary responsibilities to their owners, apparently with no long-run adverse consequences. In addition, since there is no reason why their characterizations should be unique to the pharmaceutical industry, the logic would apply to all firms. It is also unclear on what basis investment decisions would actually be made in this fictional economic world.

1.2 Taxes

Public Citizen argued that our results are not useful or valid because we did not reduce our out-of-pocket costs for the deductions taken for R&D expenditures on U.S. corporate income tax returns and for R&D tax credits. We explicitly labeled our estimates as pre-tax costs, so that neither data validity nor accuracy is an issue here. Our paper in fact contains an extensive discussion of tax issues (DHG, pp.176-180), but it is worth mentioning a few salient points here.

The primary objective of our study was to estimate the private sector economic costs needed to get a new drug from discovery to market during one period, and to compare the results to those for earlier periods. Since tax structures change over time, tax-adjusted figures can misrepresent the extent to which resource costs have changed. We do note, however, that when explicitly considering the profitability of new drug development one should consider after-tax cash flows (although the impact on profitability of changes in the tax rate is not substantial since tax rates are applied symmetrically to revenues as well as costs).[5] Indeed, two of the authors

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[5] In its discussion of the impact of reductions in the corporate income tax rate the OTA noted, "It also raised the after-tax revenues from products resulting from the R&D, so the importance of taxes is not nearly as great when measuring net R&D returns, rather than R&D costs in isolation." (OTA, 1993, p.68).

have done so in rate of return studies (Grabowski and Vernon, 1990; Grabowski and Vernon, 1994; Grabowski et al., 2002).

However, even if the intent is to measure the effective R&D cost to firms, as a stand-alone measure of R&D costs the approach advocated by Public Citizen (2001) is highly misleading. In particular, it suggests that the deductions for R&D expenses allowed on corporate income tax statements are really tax breaks, whereby the public defrays a substantial amount of a company's costs.[6] This corporate welfare view of the R&D income tax deduction (which is implicit in Public Citizen, 2001) is erroneous. The corporate income tax must be understood as a tax on net income (i.e., corporate accounting *profits*), not gross income. Deducting R&D and other costs from revenues is just part of the method by which the targeted tax base (profits) is determined. Although Public Citizen and others have characterized company deductions for R&D costs as an avoidance of taxes, since the corporate income tax is a profits tax by deducting business costs firms end up paying what they were supposed to pay in taxes.

Alternatively, R&D tax credits (which apply to all industries) are subsidies designed to spur the growth of industrial R&D. However, as noted in DHG, it is difficult to include them with real precision in the types of estimates in which we were interested, and they appear, in any event, to have not been very financially significant for the type of firm that we analyzed. As reported in our paper, recent audited financial data for so-called Big Pharma firms suggests that realized R&D tax credits have been on the order of 2% of R&D expenditures. In addition, analysis of Congressional Research Service (CRS) data on orphan drug tax credits indicates that in aggregate these credits are much less empirically significant for Big Pharma firms than are even the R&D tax credits (DHG, p.175).

Whether opportunity costs should be ignored or whether corporate income tax deductions should be included in R&D cost estimates, are questions that have nothing to do with the validity of our underlying cost data. On the other hand, in theory, Public Citizen's second approach to estimating drug development costs could reflect on data validity. However, their uses of U.S. industry trade association (PhRMA) R&D expenditure and FDA approvals data are deeply flawed.

1.3 Incomplete and mismatched data

Public Citizen (2001) presents the ratio of average annual aggregate industry domestic R&D expenditures reported by PhRMA for 1988-1994 to the average annual number of FDA new drug application (NDA) approvals for 1994-2000 (thus incorporating a six-year lag between expenditures and approvals).[7] This yields a figure of $108 million as an estimate of pre-tax out-of-pocket cost per approval. Both the numerator and denominator of this ratio are seriously biased in ways that underestimate costs.

Nearly all, if not all, of the domestic R&D expenditures of PhRMA-member firms are spent on drugs that they hope will get approved in the United States, the industry's major national market. Therefore, associating all domestic industry R&D with U.S. drug approvals, whether or not that R&D was ultimately successful in meeting its original goals, is a reasonable approximation. Public Citizen's main calculation, however, used *only* PhRMA's reported domestic R&D expenditures in the numerator. They therefore excluded the significant amount of member firm R&D expenditures that are spent abroad on discovery, preclinical development,

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[6] This discussion abstracts from any second-order effects resulting from issues related to the timing of tax payments associated with the expensing of expenditures on intangible capital, such as with pharmaceutical R&D, as discussed in DHG (p.174).

[7] Public Citizen reported on earlier seven-year periods, but since the average approval data for our sample was in 1997, the 1994-2000 approvals period is the one most relevant to our current study.

and clinical development prior to U.S. new drug approval.[8] It is perhaps even more important to realize that the PhRMA data apply only to full members of that trade association. Thus, the PhRMA data will not include the R&D expenditures of associate member or non-member firms on drugs that they license to PhRMA full member firms or, for that matter, on drugs that they take to market themselves.

While the numerator in the Public Citizen calculation is seriously underestimated, the denominator is substantially biased upward, thus further biasing their cost figure downward. Public Citizen includes in its denominator the NDA approvals of *all* companies. It erroneously relates those approvals, however, to just the R&D expenditures of firms that were full members of PhRMA. As an example of the magnitude of the problem, examination of the therapeutic new molecular entities (NMEs) approved during 1994 to 2000 shows that 29% of these approvals were obtained by firms that were not full members of PhRMA.[9]

A proper comparison to our estimate of out-of-pocket pre-tax cost per approved drug ($403 million in year 2000 dollars) using aggregated expenditure and approvals data would use the R&D expenditures spent on new self-originated drugs prior to original approval for a given set of firms and the original self-originated drug approvals for those same firms, as we did in our study (DHG, pp.179-180, Appendix B). Public Citizen's report did have a pre-tax cost calculation for all NMEs ($227 million for 1994 to 2000 approvals). This figure is biased downward for three reasons. First, they used, as they did for their preferred cost measure, only the domestic R&D expenditures of PhRMA member firms. Second, they inexplicably reduced

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[8] In a separate set of calculations in one of their appendices, Public Citizen added the foreign R&D expenditures that PhRMA collects to its domestic R&D expenditures, resulting in a pre-tax cost of $132 million. However, the PhRMA data on foreign expenditures are only for a portion of their membership (U.S.-owned firms).
[9] For purposes here, this is a conservative figure. Some firms are relatively recent members of the association, while others have left and returned to membership. A firm was counted here as a PhRMA firm if it was a member prior to the year of approval, even if it was not a member at the time of approval.

the domestic R&D expenditure figure by multiplying it by the share of expenditures for new self-originated drugs taken from DHGL, even though they used FDA totals for all NME approvals (self-originated and licensed) in the denominator. Third, they did not restrict approvals in their denominator to firms that were full members of PhRMA. Although cruder than the validation check in our study, one can, however, adjust their calculations to correct these errors and obtain a range that supports our out-of-pocket cost estimate ($360 million to $567 million).[10]

1.4 Unit of observation: NME versus NDA

Finally, given the claims that have been made in Public Citizen (2001) and elsewhere (e.g., Relman and Angell, 2002; Angell, 2004) that in essence our estimates apply just to drugs "which require the most expensive types of research" (Public Citizen, 2001, p.3), it is worth examining the propriety of reporting an average cost figure that uses an NDA approval (as opposed to an NME approval) as the unit of observation. NME approvals are only a fraction of all NDA approvals. There are several reasons (both technical and conceptual) why spreading R&D expenditures over the FDA totals for NDAs is inappropriate.

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[10] For a lower bound, we first take their PhRMA figure for domestic R&D expenditures without reducing it to cover just self-originated drugs, although we do reduce the figure to 83.5% of the total since this is the share of R&D expenditures spent on new drugs (self-originated plus licensed or otherwise acquired) as reported by PhRMA for 1988 to 1994. Next, in the denominator we use 71.2% of the total number of FDA NME approvals for 1994 to 2000 to count only the approvals of PhRMA member firms. This yields a pre-tax cost per approval of $360 million. For an upper bound, we use an estimate of the foreign expenditures of all PhRMA member firms (not just the U.S.-owned firms). PhRMA reported such a total for one year (2000). This figure indicates that domestic expenditures are 63.5% of total worldwide expenditures. It has been suggested that R&D has been shifting over time to the United States. If so, the U.S. share for the entire period analyzed would be lower than 63.5%. In addition, CMR International estimated that the United States accounted for 44% of global pharmaceutical R&D expenditures in 2000 (PAREXEL, 2002). However, the CMR survey firms were likely more foreign-based than are the PhRMA member firms. Using the 63.5% share results in an upper bound for cost per approved drug of $567 million. It should also be noted that the $360 million to $567 million range for all NME approvals was calculated without counting the expenditures on drugs licensed to PhRMA members that were incurred by firms that were not full members of PhRMA. Some of the PhRMA member firm R&D expenditures could also have been incurred on drugs that they licensed to non-member or associate member firms. However, for the period analyzed, PhRMA full member firms were much more likely to in-license drugs from non-member or associate member firms than they were to out-license drugs to non-member or associate member firms.

Counting applications approved by the FDA is not at all the same as counting new drugs in any meaningful sense. Despite the suggestive nomenclature, the FDA data on NDA approvals covers a hodgepodge of widely differing types of regulatory actions.[11] Aside from NMEs (products containing active ingredients that have never been approved for marketing), the NDA data apply to approvals for new salts or esters, new formulations or new indications[12] for existing drugs, new combinations (where all active ingredients have been previously approved), a new manufacturer for an existing drug, and very old drugs that have been marketed without an approved NDA. All non-NME approvals are for drugs (i.e., active ingredients) that have already reached the marketplace, and some do not even represent new drug products.

One of the authors (DiMasi) is currently engaged in a project to examine the nature of and trends in the non-NME NDA approvals made by the FDA over the last several decades. At this writing data are still being collected, but we can report some of the findings for the last few years. Of the 2001 to 2003 non-NME approvals, 53% were for drugs that were first approved more than 14.5 years earlier, 40% were first approved more than 20 years earlier, and one-third were first approved more than 25 years earlier.[13] Not surprisingly, then, our analyses reveal that many of the non-NME NDA approvals were obtained by companies that had no link (i.e., through licensing, co-development, or acquisition) with respect to the drug in question to the

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[11] The FDA's focus is on processing applications related to the manufacture and use of "drug products." No one would argue that generic drug approvals herald the arrival of "new drugs" on the marketplace. Yet, generic drugs are approved via ANDAs (abbreviated new drug applications). We ought not conclude then, based on the nomenclature, that generic drugs are "new drugs" that merely happen to get approved with regulatory applications than are shorter than for other "new drugs."

[12] Most new indications are approved via a supplemental new drug application (SNDA), but some are approved via an NDA. Since 1994, the FDA has not included the new indication NDAs in their reported NDA totals. They are counted, along with the other new indication approvals, in the FDA's efficacy supplement totals.

[13] The significance of the 14.5-year threshold is that under U.S. law some of the patent life for a new drug that is lost during clinical testing and regulatory review can be restored. However, the maximum effective patent life (time since approval to loss of patent protection) that is allowed with patent term restoration is 14 years. An additional six months can be obtained for testing in pediatric populations. Average effective patent lifetime for drugs first approved from the mid-1980s to the mid-1990s was 10 to 12 years (Grabowski, 1996; Shulman et al., 1999). Thus,

firm that sponsored the original NME (43% of the 2001 to 2003 approvals). For the most part, the unrelated firms are generally small specialty pharmaceutical firms and generic drug manufacturers. In addition, some of the approvals are for drugs that are over-the-counter (OTC) or for Rx-to-OTC switches (8% of the 2001 to 2003 approvals).[14] Thus, given the nature of many of the non-NME NDA approvals, the time frames involved, and the provenances of these approvals, linking all NDA approvals in a period to PhRMA member firm R&D expenditures just six years prior to the approvals, as Public Citizen did, is grossly technically inappropriate.

Aside from technical problems associated with the indiscriminate use of the annual FDA totals on NDA approvals, there is a conceptual problem with averaging over all NDA approvals. The unit of observation for our estimates is a drug (active ingredient), not a drug product. Firms typically offer drugs in many different product presentations. Many NME approvals, in fact, cover a number of different strengths of a drug, each potentially sold at a different price and serving different consumer needs. Some NME approvals also cover several formulations.

Most of the non-NME NDA approvals are for new formulations of existing drugs and combinations of already-approved active ingredients, but many of these approvals simply reflect the firm filling out its product line to better serve consumer needs (e.g., oral solutions for children and others who have difficulty swallowing tablets or capsules). In any event, these approvals represent *incremental* additions and improvements to the product lines for existing drugs. These approvals concern new "drug products", not new drugs.

While the *incremental* costs associated with particular types of product line extensions are of some interest (mainly to developers), the extensions should not be treated alongside NME

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it is likely that the many of the non-NME NDA approvals are for drugs that were off-patent long before the non-NME approval.

approvals as separate occurrences of the same unit of observation. The costs of *incremental* additions to product lines are usually significantly lower than they otherwise would be because many activities and investigations need not be repeated, and the knowledge generated by previous development of the drug will inform the firm of approaches that will likely not be fruitful. The cost of obtaining a non-NME NDA approval is therefore closely linked to the cost of obtaining the original NME approval. One cannot develop a new formulation without first having spent funds on discovering and developing the drug in its original formulation.

We believe that the best way to deal with R&D on line extensions is to use the active ingredient as the unit of observation and consider costs incurred for that unit over the entire lifecycle of the drug.[15] This is also the way that drug companies view the process. One can usefully divide expenditures into costs incurred prior to and subsequent to the first approval of a drug. We did so in DHG and found an average capitalized cost per approved drug (not drug product) over the entire drug lifecycle of $897 million (with post-approval costs that are $140 million out-of-pocket and $95 million on a capitalized basis).[16]

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[14] The PhRMA R&D expenditure data are for ethical pharmaceuticals only. These are prescription drugs and the small set of drugs that are available without a physician's prescription but which must be obtained through interaction with a pharmacist. R&D expenditures on standard OTC products are not included in the PhRMA data.

[15] To make the arguments more concrete, suppose that a firm originally got form X of a drug approved (an NME NDA approval), and later got form Y of the same drug approved (a non-NME NDA approval). It makes little sense to add the costs directly associated with X and Y and then divide by two to get an "average cost" of "new drug" development. The cost of the later form is not really separable from the cost of the original form. The direct costs associated with form Y may be much smaller than the costs associated with form X because, as noted above, the firm need not incur again many of the discovery and development costs that the firm incurred prior to the original approval. If form Y had been the one approved first, then the costs directly associated with it would have been much higher. What's more, if the firm, as a matter of strategy, had decided to wait until both forms were fully developed before it submitted an NME application, then the analyst would be dividing by one, not two, even though in both cases the firm develops the same two forms. Dividing all of a firm's R&D expenditures by all of its NDA approvals can give one highly arbitrary and radically different values depending on how many product presentations it happened to get approved in total and how many of those presentations were approved with the original NDA application versus how many happened to get approved after the original NDA approval. The only way to really make sense of the process is to view a drug in lifecycle terms.

[16] Of course, if costs are to be compared to returns, then returns should be cumulated over all product presentations of the drug (as was done in the rate of return studies noted above).

2. TB Alliance Report

Love (2003) suggests that R&D costs may be significantly less than our full capitalized cost estimate. There are numerous figures discussed in Love (2003), but the only cite therein to anything that is close to a full cost estimate is taken from a report of the Global Alliance on Tuberculosis Drug Development on the economics of tuberculosis drug development (TB Alliance, 2001). We will focus, therefore, on the TB Alliance report.

The development costs in the TB Alliance report are focused on development of a hypothetical lead drug candidate, without specified pharmacologic or chemical properties, for a tuberculosis indication. The report offers a range of $115 million to $240 million as a projected cost of developing a drug for a tuberculosis indication. For numerous reasons, the projections in the report cannot be appropriately compared to our $802 million result in DHG.

The TB Alliance report assumptions were based in large part on the development of an antibiotic (rifapentine) that received FDA approval as a treatment for tuberculosis. Drug costs can vary significantly by indication and drug type. Drug development costs for antibiotic (as opposed to some antiviral) indications are likely below average (although antibiotics are often studied in numerous indications so that total drug cost may not differ that much). In addition, rifapentine was approved as an orphan drug and developed under the accelerated approval program at the FDA. While this is likely a reasonable approach to modeling costs for a tuberculosis indication, fast-tracked orphan drug development is not representative of drug development as a whole. Development costs for such indications would typically be well below average.

In particular, the protocol in the TB Alliance report calls for just one pivotal trial. While it is quite possible to succeed in this way for a tuberculosis indication, it is very uncommon in

general for the FDA to accept just one pivotal trial. In addition, firms often rationally do more

than a couple of large-scale pivotal trials more or less in parallel to cover themselves in case

some trials fail to demonstrate the desired results. As was the case for rifapentine, a drug as

hypothesized in the report would also likely be approved with the requirement that the firm

conduct substantial phase IV testing (on the scale of a large phase III trial), thereby effectively

shifting some pre-approval costs to post-approval. In addition to the above factors, there are a

number of more micro-level costing details that suggest that the full costs of a typical drug

development program would be higher.[17]

A key distinction between what we were measuring for our studies and what the TB

Alliance report projections were designed to measure is that our estimates are costs per *drug* as

opposed to costs per *indication*. Many drugs are investigated prior to original approval for a

number of indications.[18] This distinction at least partially accounts for the most important

difference between the parameters used in the TB alliance report protocol and the historical

average experience across all drugs. The TB protocol posits 1,368 subjects in total for pre-

approval clinical testing. The average number of subjects across all pre-approval phases in DHG

is 5,303. An independent estimate puts the average number of subjects in NDAs for NMEs

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[17] First, the unit costs for many of the clinical activities in the TB Alliance report were obtained using the Medicare
Resource Based Relative Value Scale (RBRVS) reimbursement schedule. This was done for practical reasons. The
RBRVS schedule is very comprehensive. However, fees in the markets for investigators and laboratory services
used in drug development are not necessarily restricted to Medicare reimbursement rates, and may well be higher.
For example, the quality of investigators used in clinical trials may, on average, be higher than of physicians as a
whole, and they may therefore command a premium for their services. Second, the scenario laid out in the TB
Alliance report is one in which contract research organizations (CROs) conduct all of the tasks involved in
developing a drug from lead identification to regulatory approval. The costs given appear to be the resource costs of
the CROs. Not included are the internal costs associated with monitoring the CRO's activities and managing the
information obtained that manufacturers have to incur when they hire CROs. Third, CRO profits, which would also
have to be paid by manufacturers, do not appear to be included.
[18] To use a drug tested for a tuberculosis indication as an example of the extent to which this can occur, the
investigational drug SRL-172, which was studied as an adjuvant to standard tuberculosis therapy, and which failed
in that indication in three large phase III trials (PJB Publications Ltd, 2002), has, according to commercial databases
for investigational drugs (*PharmaProjects, IDdb3*), also been tested clinically in at least 14 other indications ranging
from seasonal allergic rhinitis to a variety of cancers. The drug has not been approved for any indication.

approved from 1998 to 2001 at 5,621 (PAREXEL, 2002b, pp.108-111). Thus, the average number of subjects tested for approved new drugs in general is approximately four times as large as the number posited in the TB Alliance report for a single tuberculosis indication.

Finally, the range reported in the TB Alliance report would not be comparable to our capitalized cost per-approval estimate for the simple reason that, although not apparent from the report, according to the authors of the relevant chapter costs were discounted backward to the point of lead candidate identification, rather than forward to approval (personal communication, April 2003). Thus, the range consists of projected out-of-pocket costs at one end and something less than what was actually to be expended at the other end. The interest of the authors was in examining whether tuberculosis drug development was financially viable. Their main analysis was a rate of return calculation. As long as one uses the same point in time for both projected costs and returns, then one can determine whether the process is financially viable. However, this obviously renders meaningless a comparison to an estimate that capitalizes costs forward to marketing approval.

Conclusions

The pharmaceutical R&D cost figures in two reports that have been cited as alternatives to the results in DHG are either methodologically or conceptually flawed, or they are not comparable. In the case of Public Citizen (2001), claims about pharmaceutical R&D costs are based on fallacious economic reasoning about the nature of investment in R&D and an erroneous view of the corporate income tax. In addition, Public Citizen's analyses of published industry and FDA data are seriously flawed in ways that bias the results downward substantially. A more sophisticated approach to using these data that avoids the errors inherent in Public Citizen (2001) was reported in DHG and it corroborated the cost estimates based on survey data in that study.

Similarly, a corrected version of a cruder analysis in Public Citizen (2001) also corroborates the results in DHG.

The TB Alliance report was not intended to provide an estimate of the average cost of new drug development for drug development as a whole. Our examination of the details of the report showed why average costs per new drug should be substantially higher than the projected costs for the single indication that was the focus of that report. Consequently, the figures used in the TB Alliance report are not inconsistent with our results. Attempts to compare the TB Alliance figures to our cost estimates are thus inappropriate.

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