Pharmaceutical Industry R&D Costs:
Key Findings about the Public Citizen Report

by

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SUMMARY OF KEY FINDINGS

Many of the arguments made by the Public Citizen report do not stand up to close scrutiny. In several key aspects, the Public CitizTc(pN approach deviates fromot sndard methodolog)

BACKGROUND

In July 2001, Public Citizen released a controversial new report, *Rx R&D Myths: The Case Against The Drug Industry's R&D 'Scare Card'*, arguing that the pharmaceutical industry is exaggerating the risk and cost of its R&D activities. Ernst & Young LLP was hired by Pharmaceutical Research and Manufacturers of America (PhRMA) to evaluate the Public Citizen report in light of research done by Dr. Joseph A. DiMasi of Tufts University, by the Congressional Office of Technology Assessment (OTA), and by the National Institutes of Health (NIH). This study outlines some of our key findings.

COST OF CAPITAL

Issue: Unlike other studies of pharmaceutical R&D costs (including the DiMasi and OTA studies), the Public Citizen study did not include the opportunity cost of capital in its estimates. Excluding this cost significantly lowers the Public Citizen estimates of R&D costs.

Findings: **The exclusion of the opportunity cost of capital is a shortcoming of the Public Citizen report, as it is common financial practice to account for this cost. This cost is a particularly important consideration for pharmaceutical companies, because R&D investment can be highly risky.** The justification for the Public Citizen's omission of this cost is not clear.

The cost of capital is a valid cost that must be accounted for when evaluating any investment.[1] The opportunity cost of capital must reflect the higher rate of return required for investments in risky projects. When a pharmaceutical firm's management decides (on behalf of its investors) whether to pursue an R&D project, it evaluates whether the project is a better use of capital than alternative investments. Any individual R&D project is a risky endeavor, and firms diversify their risk by pursuing multiple R&D projects at once. Investors can further diversify the risk of R&D by investing in multiple pharmaceutical firms. However, there is some risk that cannot be diversified – this is the "systematic" risk or "beta". To remain indifferent between a risk-free investment (such as T-Bills) and a riskier investment such as pharmaceutical stocks, investors require a higher rate of return reflecting the higher risk.

TAXES

Issue: The Public Citizen report argues that the true cost of R&D is the "after-tax" cost and subtracts the value of the R&D tax deduction in its estimates of the cost of pharmaceutical R&D. This is a significant departure from previous research, and one that lowers the Public Citizen estimates.

[1] See, for instance, Brealey and Myers, Principles of Corporate Finance (4th Edition), 1991: "When we measure the cost of a project, it is customary to include the cost of capital. The cost of capital – often referred to as the opportunity cost of capital -- is the expected return that is foregone by investing in a project rather than in comparable financial securities."

Findings: **The pre-tax value of pharmaceutical R&D expenditures more accurately reflects the true value of the resources that must be devoted to this activity, because the value of the associated tax deduction will vary depending on the particular financial profile of the business incurring the expense, which may be limited in its ability to take deductions.** An after-tax concept calculated at the highest corporate tax rate, like the one referred to in the Public Citizen report, may not accurately reflect the net cost of deductible business expenses for many businesses. For this reason, we do not generally talk about the "after-tax" cost of business expenses like cost of goods sold.

The tax deductibility of business expenses such as R&D works only to ensure that the revenues dedicated to these expenses are not subject to a double layer of tax. The tax code allows businesses to deduct expenses like R&D and salaries, for example, because these payments accrue to other entities that pay income tax on those revenues. These expenses are tax deductible, not to subsidize the business incurring the expense, but to avoid a double tax on the revenue streams.

Issue: The Public Citizen paper refers to the pharmaceutical industry as "lightly taxed."

Findings: **The pharmaceutical industry leads all industries in the tax it pays as a percentage of its revenues.** This means that pharmaceuticals firms pay tax on a larger portion of their revenues than firms in other sectors, on average. (See Table 1)

Table 1. Corporate Income Taxes & Total Receipts for Drugs and Other Industries
Number of Returns in thousands, Receipts and Taxes in $ Millions

	Number of Returns	Total Receipts	Total Income Tax After Credits	Tax After Credits Except Foreign Tax Credit	Taxes after Credits /Revenues	Taxes after Credits (except FTC) /Revenues
Drug Manufacturing	**3**	**$197,817**	**$5,542**	**$7,746**	**2.80%**	**3.92%**
Finance, Insurance, & Real Estate	745	$2,711,270	$54,777	$61,404	2.02%	2.26%
Transportation & Public Utilities	209	$1,330,726	$25,582	$26,381	1.92%	1.98%
Mining	33	$150,318	$2,020	$2,923	1.34%	1.94%
Manufacturing (incl. Drug Manuf.)	325	$5,177,664	$64,307	$94,619	1.24%	1.83%
Manufacturing (excl. Drug Manuf.)	323	$4,979,847	$58,765	$86,873	1.18%	1.74%
Services	1,593	$1,638,588	$12,111	$14,206	0.74%	0.87%
Agriculture, Forestry, & Fishing	163	$117,388	$599	$634	0.51%	0.54%
Wholesale & Retail Trade	1,149	$4,703,817	$21,960	$23,344	0.47%	0.50%
Construction	488	$779,014	$2,818	$2,862	0.36%	0.37%
All Industries	4,710	$16,609,707	$184,175	$226,375	1.11%	1.36%

Source: Internal Revenue Service, Statistics Of Income Corporation SourceBook Publication 1053, 1997

A Congressional Research Service (CRS) study using the same data source (IRS Corporate Source Book) shows that the industry has a lower tax burden relative to other industries when the tax burden is measured as taxes after credits as a percentage of taxable income. However, as discussed below, the effect of extensive foreign operations and general business credits mean the

effective tax rate as defined by CRS (tax after credits / taxable income) may not be the appropriate measure of tax burden for this sector.

Foreign tax credits: **The pharmaceutical industry has significant overseas activities and higher foreign tax liabilities than many other industries, and showing tax liabilities after the foreign credit distorts the results against the industry.** The tax measure used by the CRS study is "total income tax after credits", which includes the foreign tax credit. As the CRS study points out, the foreign tax credit is different from other credits in that it is not a tax benefit that lowers companies' total tax liabilities, but simply prevents double taxation for those companies with foreign tax liabilities. Presenting the tax liability after credits except the foreign tax credit shows a smaller difference between the pharmaceutical and other industries.

General business tax credits: The CRS effective tax measure also the effects of credits provided in the tax code for companies that engage in certain activities, for example, research and development and doing business in Puerto Rico. Congress enacted these tax credits to encourage certain activities by businesses, and it is important to keep these policy goals in mind when considering their effect.

The R&D credit, for example, provides incentives for firms to invest in risky research that yields valuable new technologies in a small percentage of the projects undertaken. The progress that the small percentage of successes represents, however, is immeasurably valuable.

Tax credits represent incentives that could have been provided via direct spending programs. The incentives were provided through the tax code, however, in order to minimize government bureaucracy and maximize program effectiveness. Credits should be evaluated on the basis of their overall benefits and costs, similar to direct subsidies, and not criticized as "tax avoidance" simply because they are utilized.

THE DIMASI DATA

Issue: The Public Citizen report criticizes the 1991 study by Dr. DiMasi report on the grounds that the data used were not verifiable.

Findings: **After review of the data used in the DiMasi study, the OTA cited a "substantial consistency" between aggregate R&D spending estimates and cash outlays per NCE estimated by DiMasi.** OTA concluded from the corroborative evidence available at the aggregate spending level that the estimates of cash outlays per successful NCE made by DiMasi are reasonably accurate.

In fact, the OTA's approach in its assessment of R&D costs relied on a detailed analysis of the validity of the Hansen and DiMasi studies. The OTA reviewed estimating methodologies for cash outlays, project time profiles and success rates and tested the consistency of the results with corroborative studies. Then, they examined the rate of increase in real R&D costs by looking at the major cost drivers of R&D: number of subjects in clinical trials, personnel costs and animal research costs. The OTA review did not raise serious questions about the validity of the methodology, data or assumptions used in either study.

Issue: Public Citizen claims that the DiMasi estimates may reflect the cost of marketing.

Findings: **There are no marketing costs reflected in the DiMasi estimates**, as described by the author of the study.[2] Both in his article and in an interview with E&Y, Prof. DiMasi describes the methodology as relying on micro level data on the cost and timing of new drug development through the FDA approval process, which precedes any marketing activity by the firm. He breaks the estimated cost of drug discovery into components capturing the cost incurred in the various drug development stages. None of these stages in the development of a new drug involves marketing.

NEW CHEMICAL ENTITIES (NCES)

Issue: The Public Citizen report criticizes the DiMasi study for only including New Chemical Entities (NCEs) in its estimates of the cost of R&D, arguing that this overstates the cost of R&D.

Findings: **NCEs are the most significant part of pharmaceutical R&D – they produce the largest increases in public health and lay the groundwork for follow-on products**.

NCEs are new therapeutic molecular compounds that have never previously been used or tested in humans.[3] Follow-on drugs are not included in the definition of NCEs. Such follow-on items include trials for new combinations, formulations or dosages. The OTA study validates the DiMasi approach, by pointing out that "the discovery and development of NCEs is the heart of pharmaceutical R&D and the developers of follow-on or generic products build on the knowledge produced in the course of developing them… Most of the money spent on pharmaceutical R&D goes to the discovery and development of NCEs." While it is true that NCEs are more expensive than follow-ons, it is also true that they produce the largest increases in public health.

The OTA also validates the project-level approach that examines the costs associated with developing NCEs, on the grounds that such an approach "provides the most detailed view of the costs of particular projects and overall development costs."

RISK AND "ME-TOO" DRUGS

Issue: The Public Citizen study criticizes the industry's investment in "me-too" drugs, arguing that these drugs are not as risky as pioneer drugs, and that they produce little or no therapeutic gain over existing drugs.

Findings about Me-Too Drugs: **R&D costs for "me-too" drugs may be every bit as risky and expensive as the costs for pioneer drugs. Furthermore, me-too drugs increase competition for a particular therapeutic condition, which benefits consumers.**

[2] Interview with Joseph DiMasi, August 6, 2001.

[3] NCEs should not be confused with New Drug Approvals (NDAs), which are applications seeking FDA regulatory approval to market a new product.

NCEs can be broadly classified into pioneer drugs and me-too drugs. Pioneer drugs have molecular structures or mechanisms of action that are very different from existing drugs (e.g., first to inhibit action of a certain enzyme). "Me-too" drugs work using a mechanism similar to pioneer drugs.

The existence of multiple similar therapies because of me-too drugs *increases* competition in a particular market segment, giving consumers more choices and lower prices. The OTA points out that "much of the R&D on me-too drugs is *not imitative but competitive.* The race has one winner and often a field of followers. The R&D costs of those who lose the race but manage ultimately to produce a product may be *as high or even higher than the costs of developing the pioneer compound*." [emphasis added]

The Public Citizen report implied that the pharmaceutical industry is misrepresenting the risk of its R&D, supposedly because R&D on "me-too" drugs is very lucrative but not very risky. Further consideration, however, reveals that while R&D on some "me-too" drugs may be lower than that of pioneer drugs, it is also likely to yield lower returns. In many cases, the situation is exactly the opposite of that portrayed by the Public Citizen report: R&D for me-too drugs could be more expensive and less lucrative than for pioneer drugs.

Table 2. Summary of R&D Drug Types

Type of Drug	Benefit to consumers
NCEs: Pioneer	Large increases in public health; new treatments
NCEs: "Me-too"	Increased competition for pioneer drugs; more choices & lower prices
Follow-on	New formulations, delivery systems

Findings about R&D Risk: **Pharmaceutical R&D represents a risky process, and investments in this process bear that risk.** For every drug successfully brought to market, there are 5,000-10,000 unsuccessful compounds screened and 250 that undergo preclinical testing.[4] The cost of these failed projects must be considered when evaluating the costs of bringing a successful therapy to market.

The NIH describes the route to drug discovery as "unpredictable". The decision to continue with a project, made at several stages in the development of a therapy, has to consider several risk factors, including: therapeutic benefits; frequency and severity of adverse reactions; and the cost of production, distribution and marketing.

The low probability of proceeding from the pre-clinical phase to new drug approval (NDA) illustrates the high risk inherent in pharmaceutical R&D. Only two percent of projects in the pre-clinical phase are expected to make it to Phase I testing and, of these, only one in five are likely to be approved. The OTA report reveals that over a 17 year period, approximately 14 percent of self-originated NCEs first investigated in humans between 1964 and 1975 were approved.

[4] PhRMA, Pharmaceutical Industry Profile 2001.

The return on R&D remains subject to variation in several key factors. For instance, the OTA report finds that "dollar returns on R&D are highly volatile over time… changes in R&D costs, tax rates, and revenues from new drugs are the most important factors influencing net returns."

The OTA report also indicates that there is significant variation in the cost of pharmaceutical R&D. "The cost of bringing a new drug to market is very sensitive to changes in science and technology, shifts in the kinds of drugs under development and changes in the regulatory environment. All of these changes are occurring fast. Consequently, it is impossible to predict the cost of bringing a new drug to market today from estimated costs for drugs whose development began more than a decade ago."

CHANGES IN THE COST OF R&D

Issue: The Public Citizen report claims that changes in the FDA approval process and the development of new basic research technologies have *reduced* the cost of pharmaceutical R&D over the period since the DiMasi estimates were calculated.

Findings: The Public Citizen study fails to mention that **there are several factors that have *increased* the cost of R&D**, including:

- Complex diseases require longer and more expensive clinical trials.
- Attrition rates for R&D projects, the source of great risk in these investments, remain high. For instance, DiMasi finds that attrition rates were fairly constant for drugs introduced from 1981 through 1992.
- The development of new biotechnologies that are being integrated by pharmaceutical firms may yield economies in the future, but in the near-term the development, acquisition, and implementation of these new technologies adds large fixed and variable costs to the R&D process.

GOVERNMENT RESEARCH

Issue: The Public Citizen report argues that industry R&D risks and costs are often significantly reduced by taxpayer-funded research, which has helped launch the most medically important drugs in recent years and many of the best-selling drugs, including all of the top five sellers in one recent year surveyed (1995).

Findings: **The pharmaceutical industry and the public sector play important complimentary roles in identifying and developing new drugs.**

A recent report by the National Institutes of Health (NIH) entitled "NIH Contributions to Pharmaceutical Development" describes the contributions of public and industry research as "complimentary". Both public and private research play necessary roles in finding, developing and bringing a new therapy to market. Academic scientists work out the biology of a disease, while subsequent research to identify, develop and test new drugs is performed by the industry. NIH describes the industry's role in the R&D process: "Once a potential drug is discovered, industry scientists conduct extensive in vitro and animal tests until they are ready to patent the invention and publish the results. Then, further studies by the company and academic

researchers on the drug's mechanism of action and its effects on animals, and, eventually, on human patients, fits into a framework of continuing basic and applied advances."

The NIH also states that "private industry does play a large and growing role in medical research. By 1994, industry accounted for over half of the total national investment in medical research." Again, the role of industry compliments the role of publicly-funded research. While public investment in pharmaceutical research is often aimed at uncovering the biological mechanisms of disease, most of the private investment funds applied research and product development.

One example of the synergies of public and private research is combinatorial chemistry. This term refers to a collection of methods to produce enormous numbers of molecules in an orderly, tagged sequence. These technologies speed up empirical drug searches by generating a diversity of compounds to screen for a lead. Although these methods have their roots in publicly-funded basic research, they were designed and developed by industry scientists. Industry scientists are also developing molecular structure modeling, an approach to enhance rational drug research and design.

CONCLUSIONS

Many of the arguments made by the Public Citizen report do not stand up to close scrutiny. In several key aspects, the Public Citizen approach deviates from standard methodologies adopted by previous research and the financial and accounting communities. On many issues, the report presents selective evidence and ignores strong evidence to the contrary. These methodological shortcomings cause Public Citizen to underestimate the cost of pharmaceutical R&D.