Expert Report JL-RND

Evidence Regarding Research and Development Investments in Innovative and Non-Innovative Medicines
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1. Introduction

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This report reviews the evidence of the costs of private sector drug development, the nature of private R&D flows, and alternative mechanisms that governments may consider when seeking to support innovation in medicines.

2. Empirical Estimates of Drug Development Costs

2.1 The Tufts Study

[REDACTED]

The Tufts report placed the cost of bringing a new drug to market at $802 million. This estimate includes the average cost of both pre-clinical and clinical studies, up to the time of receiving FDA marketing approval. "Out-of-pocket" costs on individual projects are included, as are allowances for failed projects, and the opportunity cost of capital. Roughly half the total -- $399 million -- was allocated to the opportunity cost of capital.

Before the report was published in an academic journal, it was presented to the press at a November 30, 2001 briefing organized by Merck, featuring a speech by Raymond V. Gilmartin, the company CEO.[1] In 2003, after countless news reports and citations, the study was finally published in an academic journal.[2] The authors of the Tufts study were Joseph A. DiMasi of Tufts, Ronald W. Hansen of the University of Rochester, and Henry G. Grabowski of Duke University, three academic researchers that work closely with the research-based pharmaceutical industry. Much of the work

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[1] Gardiner Harris, *"Health Cost of Developing New Medicine Swelled To $802 Million, Research Study Reports," The Wall Street JournalDATE*. "Merck & Co. Chairman and Chief Executive Raymond V. Gilmartin attended the unveiling of the Tufts data at a Philadelphia hotel and said increased clinical costs stem from demands by managed-care buyers that drug companies prove the value of their drugs in larger and longer trials. . . Dr. DiMasi, lead author of the Tufts Study, has been issuing research-cost estimates for years based upon proprietary surveys of top drug companies. His numbers are routinely cited by industry backers to justify the ever-rising prices of new drugs. . . . Mr. Gilmartin also argued that, given the enormous cost of research, big pharmaceuticals companies, not small biotechnology firms, are essential for developing medicines. He also said that patent-protection laws, which have come under attack by some drug-company critics, are vital to encouraging and protecting such huge investments."

[2] Joseph A. DiMasi, Ronald W. Hansen, Henry G. Grabowski, "The price of innovation: new estimates of drug development costs," *Journal of Health Economics* 22 (2003) 151–185.

at the Tufts CSDD is funded by pharmaceutical industry corporate sponsors,[3] and work from the CSDD and the study authors is often used to support industry positions on regulatory, intellectual property and pricing policies.

The Tufts Study estimates of the costs of Pre-clinical, human-use Phase I, II and III clinical trials and long-term animal trials are summarized in Table RND 2.1-1.

Table RND 2.1-1: Tufts study estimate of costs of development of self-originated New Chemical Entity

	Out of pocket cost of trials	Probability of product entering the Phase to receive FDA approval	Cost adjusted for risk of failures	Cost adjusted for risk, and capital costs at 11 percent real return
Pre Clinical			$ 121.0	$ 335.0
Clinical				
Phase I	$ 15.2	.215	$ 70.7	$ 141.4
Phase II	$ 23.5	.303	$ 77.6	$ 139.7
Phase III	$ 86.3	.685	$ 126.0	$ 163.9
Total human use clinical trials	$ 125.0		$ 281.9	$ 444.9
Animal Studies	$ 5.2	.685	$ 7.60	$ 13.7
Total pre-clinical and clinical costs			$ 402.9	$ 793.7

Source: Joseph A. DiMasi, Ronald W. Hansen, Henry G. Grabowski, "The price of innovation: new estimates of drug development costs," *Journal of Health Economics 22 (2003) 151–185.*

The key points of the Tufts estimates are as follows:

1. Every product is assumed to be self-originated new chemical entities, with negligible benefits from government funding sources.
2. The approximate time from the first pre-clinical research to approval is 12 years.
3. The entire estimate is driven by the data for clinical costs.
4. The average size of human-use clinical trials (Phase I, II and III) in the sample is 5,303. [4]

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[3] Ceci Connolly, "Price Tag for a New Drug: $802 Million: Findings of Tufts University Study Are Disputed by Several Watchdog Groups," *Washington Post*, December 1, 2001, "The center receives much of its funding from the industry, although DiMasi, said the money comes 'with no strings attached.' Its Web site has a section dedicated to praise from industry executives." Naomi Aoki, "R&D costs for drugs skyrocket, study says: Tufts Center estimates amount up threefold from a decade ago," *Boston Globe,* December 1, 2001, "The Tufts study was funded out of the Center's general budget. The Center receives 65 percent of its support from industry-related sources."

[4] The size of the trials in the Tufts study is reported in Footnote 41.

5. The survey respondents claim that the average per-patient cost of clinical trials is $23,572. ($83,902 when risk and capital costs are added).

6. The average time from synthesis of a compound to initial human testing for self-originated drugs was 4.33 years.

7. The approximate the lag time between pre-clinical and clinical expenditures for a representative new drug was approximately 5 years.

8. The time between the start of clinical testing to marketing approval was estimated to be 7.5 years.

9. The overall probability of success for products entering Phase I clinical trials was .215, for phase II .303, and for Phase III trials .685.

10. With an 11 percent real return, the opportunity cost of capital is captured with a multiplier of 2.0 for phase I trials, 1.8 for phase II trials, 1.3 for phase III trials, 1.8 for long-term animal studies, and 2.77 for pre-clinical research.

11. Pre-clinical costs are always assumed to be 30 percent of the total risk-adjusted outlays, which come to about 43 percent of outlays on clinical trials.

12. In US dollar terms, pre-clinical outlays are $121 million before capital costs and $335 million after capital costs.

13. The average cost of pre-approval human use clinical trials (Phase I, II and III) are estimated to $125 million in cash outlays for a project that is approved, or $282 million when adjusted for the risk of failures, $445 million when the both risk and the opportunity cost of capital are added.

As is evident from Table RND 2.1- 1, the Tufts study adjustments for risk and the cost of capital are quite important. This is most evident from the Phase I costs, which are reported as $15.2 million out-of-pocket, $70.7 million when adjusted for the risk of failure, and $141.4 million when adjusted both for risk and the cost of capital. There is considerable confusion among many policy makers and journalists over the Tufts Study figures; problems typically arise when people try to comprehend the meaning of a "cost" that already reflects the risks of failures and *opportunity cost* of capital. Some persons *(not the authors)* deliberately report the higher numbers, as if they represent actual company out-of-pocket outlays on a particular product, implying that the firm needed to return multiples of the higher number as reward for risk and investment return. This is of course double counting, since both risk (cost of failures) and the opportunity cost of capital (11 percent real) have already been included, and indeed, these are the factors that drive the estimates to such lofty heights.

There is controversy regarding several of the empirical findings, both in terms of the estimates themselves and also in terms of relevance to particular situations. The "average" size of the trials is considerably larger than the numbers cited by the FDA in its approval letters,[5] and the costs per patient are quite a bit higher than the costs per patient reported by the National Institutes of Health or the World Health Organisation for trials they support, and a number of private estimates of the costs of outsourced clinical trials (see below) and they are far higher than earlier estimates by the same authors.[6] The authors of the study have not disclosed the underlying data,

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[5] The FDA approval letters sometimes under-report the total number of patients in trials.

[6] Referring to both human use and animal trials, DiMasi, et. al. report, "Aggregating across phases, we find that the out-of-pocket clinical period cost per approved new drug . . . are more than four-fold higher than those we found in our previous study." DiMasi (2003).

which they collected from 10 large pharmaceutical companies. There is evidence to suggest that the costs of clinical trials reported in the Tufts study may be overstated or at least are not representative of the average products approved by the FDA, and indeed it is not clear that the authors even claim that the costs are representative of average drug development costs.[7] Finally, it is important to recognize that the costs of drug development vary considerably between drugs and classes of drugs, and several key assumptions in the Tufts report may be quite unreasonable when applied to particular situations, such as products licensed from third parties, products that have benefited from government support, Orphan products, or products that have received fast-track regulatory approval.

The Tufts study also reports that, in addition to risk-adjusted cash outlays of $403 million spent on pre-clinical and clinical studies to obtain product approval, another $140 million will be spent later on post-approval clinical studies, many of them related to marketing of products. Thus, the study estimates that 26 percent of all pre-clinical and clinical research ($140 of $543 million) *and 33 percent of all outlays on clinical trials ($140 of $422 million),* are spent on drugs already on the market.

2.2 The TB Alliance Study of Drug Development Costs

Other estimates of the costs of the drug development, including estimates based on the industry's self-reported data on drug development, suggest R&D costs are much lower than the Tufts estimate. One such estimate comes from the 168-page TB Alliance report: *The Economics of TB Drug Development,* which is less well known than the Tufts Study, but considerably more detailed in terms of data.[8] The 2001 TB Alliance Study was financed by the National Institute of Allergy and Infectious Diseases (NIAID) of the U.S. National Institutes of Health (NIH), includes prefaces by Dr. Gro Harlem Brundtland, the former Director-General of the World Health Organisation (WHO), and Dr. Harvey E. Bale, Jr., the Director-General International Federation of Pharmaceutical Manufacturers Associations (IFPMA),[9] and was prepared under supervision of Giorgio Roscigno, a former executive at Aventis, and Doris J. Rouse and Nancy Pekar of Research Triangle Institute (RTI).

The TB Alliance study estimated the cost of drug development as $115 to $240 million, including the costs of failures. While the TB Alliance study tracked some of the Tufts assumptions, it also contained significant differences. Most notable were the lower estimates of the costs of clinical trials. The Tufts study had estimated $125 million as the out-of-pocket costs for human-use clinical trials, before adjustments for risk or capital costs. The TB Alliance study says "In an established economy, clinical trials for an NCE to treat TB are estimated to cost $26.6 million . . . Comparable studies in a developing economy are estimated to cost $9.9 million." The TB Alliance study provides a larger number of examples of actual and possible clinical trial costs,

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[7] On 4 December 2001, Joesph DiMasi said, "It should also be noted that our study was based on the R&D experiences of major traditional pharmaceutical firms," distinguishing for example, the study's sample from the experiences of ". . . small biotech and niche pharmaceutical firms."
http://lists.essential.org/pipermail/ip-health/2001-December/002500.html (accessed 1 August 2003).
[8] Global Alliance for TB Drug Development, *The Economics of TB Drug Development,* October 2001.
[9] Harvey Bale generally praised the TB Alliance report, but also noted the controversy over its estimates of the costs of drug development.

with very detailed explanations of the fixed and variable costs for different types of trials. On a per-patient basis, the TB Alliance appendices provide examples of trials that cost as little as $644 per patient to those that cost more than $22,000 per patient, depending upon the survey design and the location of the tests. In the base case, the total number of patients is assumed to be 1,368, roughly a quarter of the "average" estimated in the Tufts study.

The TB Alliance study based the design of the trials on US regulatory requirements and the WHO/IFMPA regulatory harmonization recommendations "in line with the ICH's good clinical practice (GCP) standards. . . . for a new chemical entity for the treatment of active TB."

2.3 Orphan Drug Development

Another measure of the cost of R&D comes from analysis of company data submitted to get tax credits in the United States for Orphan drug development. This data too suggests costs are far below the levels estimated in the Tufts Study.

The United States classifies any treatment for an indication that afflicts 200,000 or fewer patients in the United States as an Orphan Product. The Orphan designation has significant economic benefits, including a broad seven-year marketing exclusivity and a 50 percent tax credit applied to qualifying clinical trials. The Orphan Product tax credit is normally limited to expenditures on clinical trials in the United States, although a taxpayer can claim the credit for foreign trials if there is "an insufficient testing population in the United States."

This tax credit first went into effect in 1982, was suspended temporarily from 1994 to 1996, and is now permanent. Among the HIV/AIDS drugs to receive an Orphan designation and FDA approval for marketing during this period was Zidovudine (AZT), marketed as Retrovir® by GlaxoSmithKline. AZT received an Orphan designation in July 1985 and FDA marketing approval in March 1987.

Under the Orphan Drug Act, the orphan designation is given for a specific indication. Thus any one drug may receive more than one orphan designation, or be approved for use for both Orphan and non-orphan uses. The credit also applies to new uses for existing products, such as the Orphan designation for the use of Epogen for HIV/AIDS, or Paclitaxel to treat AIDS-related Kaposi's sarcoma.

A 2001 study by CPTech, found that there were 1,084 orphan designations since the program began. Of the 1,084 orphan designations, some 20 per cent (218 of the 1,084) had received FDA marketing approval. This is roughly the same approval rate as is the case for all drugs that enter Phase I human use testing in the US. Of the 1,084 Orphan designations, 74 were for treatment of HIV/AIDS. Of these, 24 per cent (18 of 74) had received FDA marketing approval.

Table RND 2.3-1 provides data obtained from the Orphan Drug Tax Credit on the outlays on clinical trials for orphan products. For products eligible for the orphan drug tax credit, total pre-tax outlays on clinical trials were $538.4 million from 1998 to 2000. During this time the FDA approved 49 new Orphan indications and 16 new chemical entities. The outlays per new orphan indication were $11 million before the

orphan tax credit, and $5.5 million after the orphan tax credit. Per NCE approval, the outlays were $34 million   before the tax credit, and $16.8 million after the tax credit.

Table 2.3-1: Pre-Tax Cost of Trials for Orphan Products: FDA approvals of Orphan Indications and Orphan NMEs *(Millions of USD)*

	1998	1999	2000	total
Orphan Credit	$ 80.4	$ 109.4	$ 79.4	$ 269.2
Pre-tax cost of trials	$ 160.8	$ 218.9	$ 158.8	$ 538.4
FDA Marketing Approvals	Orphan Indications			49
	Orphan NME			16

Cost of Trials (Before Orphan Tax Credit) per FDA Marketing Approval

Per Orphan Indication		$ 10.99
Per Orphan NME		$ 33.65

Cost of Trials (Net of Orphan Drug Tax Credit) per FDA Marketing Approval

Per Orphan Indication		$5.5
Per Orphan NME		$16.8

Source: IRS, FDA

As noted, the Orphan Drug Tax Credit applies to both new indications as well as NMEs. The trials to support FDA approval for a new indication are generally less expensive than the cost of obtaining FDA approval for a NME. It is not possible to obtain separate data on new indications and NMEs (the IRS combines the data). The cost of trials for a NME only are somewhere between the simple averages of based upon the number of indications or NMEs.

The tax credit is available regardless of whether or not the product succeeds in obtaining FDA approval. The cost per FDA approval thus captures the clinical costs of both the successful *and* the unsuccessful products. Before the tax credit, this is somewhere between $11 and $34 million.[10]   The comparable number from the Tufts study is the risk-adjusted costs of clinical trials, which are $282 million in the Tufts study.

Note that the $282 million figure from the Tufts study is reported as the *average* for a single drug, and yet it is more than half of the (pre-credit) amount spent during a three year period when the FDA approved 49 new orphan indications (including 16 NME orphans).

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[10] $11 million figure if the average cost of NMEs are the same as the average cost of FDA approvals for new indications, or $34 million figure if the average costs of new indications are zero.

The evidence from the Orphan drug tax credit is that for at least one class of drugs, the average cost of trials is far smaller than the Tufts study estimate.

How important are Orphan products? As noted above, a number of HIV products have benefited from Orphan designations. A 2000 study by two other Tufts researchers, Kenneth Kaitin and Elaine Healy, looked at 110 FDA New Chemical Entities (NCEs) approved for marketing by the FDA from 1996 to 1998. Of the 110 NCEs, 18 had been designated as Orphans, or about one sixth of all NCEs for that period.[11] Over the next four years, the ratio was 16 of 103. For the period 1996 to 2002, 16 percent of all NCEs were Orphan products. For severe illnesses, the share of Orphan products is higher.

2.4   Parexel Analysis of Size of Clinical Trials

Parexel's annual *Pharmaceutical R&D Statistical Sourcebook* reports a number of statistics on the number of patents in clinical trials. One set of statistics is a survey of 64 of 116 New Molecular Entities (NMEs) approved by the US FDA from 1998 to 2001. The Parexel survey only includes products for which Parexel could confirm the size of total Phase I through Phase III clinical enrollments. Many of the excluded products are orphan drugs. For example, 7 of the 13 excluded products in 1998 were classified as orphan drugs, suggesting the Parexel survey overestimates the size of trials.

Table RND 2.4-1 : Mean and median number of patents in clinical trials: FDA NME approvals 1998 - 2001

	2001	2000	1999	1998
Mean Patients Per NDA	5,144	6,659*	4,980	5,697
Median Patients per NDA	4,186	3,840	5,435	4,325
Range	832-17,000	1,345 - 35,696	202 - 14,300	212 - 16,000
Number of NME in sample	12 of 24	16 of 27	19 of 35	17 of 30

   * The mean in 2000 drops to 4,723 without Mobic.

Source: Parexel Pharmaceutical R&D Statistical Sourcebook 2002, page 108.

2.5 October 2001 FDA Study of Clinical Trials.

An October 2001 Study by the US FDA looked at the number of trials and patients in clinical studies used to support the approval of New Molecular Entities. Looking at the number of patients described by the medical officer as being enrolled in clinical studies, The FDA study found that 493,347 patients were enrolled in clinical studies for the 185 NMEs approved from 1995 to 1999. The average number of patients for each approved NME was 2,667. There were an average of 14 clinical studies for each NME, and an average of 191 patients in each study.

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[11] Kenneth I. Kaitin and Elaine M. Healy, "The New Drug Approvals of 1996, 1997, and 1998; Drug Development Trends in the User Fee Era," *Drug Information Journal*, Vol. 34, pp. 1-14, 2000.

2.6 The PERI Survey of development costs

A much different estimate of drug development costs was presented by the Pharmaceutical Education and Research Institute (PERI).   PERI looked at 117 development projects at 20 PhRMA member companies, ranging in size from small biotech firms to the largest big pharma companies.[12]   The survey found that it look 7.1 years in total to complete all four stages of drug development (pre-clinical, Phase I, Phase II and Phase III), and that the average total outlays on a successful project was $75.4 million, broken down as follows:

Table RND 2.6-1: Average Time and Spending per project

	Pre-Clinical	Phase I	Phase II	Phase III	Total
Spending	$5.9 million	$7.3 million	$18.9 million	$43.3 million	$ 75.4million
Time	1.6 years	1.5 years	1.5 years	2.5 years	7.1 years

The PERI study also found very large differences in the size of the outlays by firm size. The average annual outlays on project development were less than half for the small and very small firms.

2.7 R.W. Johnson PRI Estimates of the cost per patient for promotional Media

One growing element of clinical trials costs relates to advertising and promotional media to recruit patients, an item particularly important for trials on products for which there are existing treatments, and patients need encouragement to participate. R.W. Johnson PRI reports that advertising and promotional costs per patient has increased from $1,200 to $1,800 in 1997, to $3,500 to $5,000 in 2001.[13]

2.8 Other Per Patient Costs for Trials

BMS oncology trials

Robert Kramer, Vice President for Oncology Drug Discovery and New Business Ventures. The average cost of oncology trials is $10,000 per patient.[14]

NIH DCP Cooperative Group Treatment Trials and Funding, 1993 to 1999

In 1999 the National Institutes of Health reported the cost per trial and cost per patient for oncology trials funded by the NIH DCP Cooperative Group Treatment Trials.

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[12] *Project Management in Pharmaceutical Industry: A survey of Perceived Success Factors 1995-1996* . PERI.
[13] *Parexel Pharmaceutical R&D Statistical Sourcebook 2002*, page 117.
[14] *Parexel Pharmaceutical R&D Statistical Sourcebook 2002*, page 117.

Table RND 2.8-1: NIH DCP Cooperative Group Treatment Trials and Funding, 1993 to 1999

FISCAL YEAR	Number of trials	Number of of Accruals	Cost of Trials	Cost per patient	Cost per trial
FY93	478	21018	$ 81,159,000	$ 3,861	$ 169,789
FY94	477	18788	$ 82,362,000	$ 4,384	$ 172,667
FY95	445	17548	$ 82,327,000	$ 4,692	$ 185,004
FY96	428	18305	$ 96,969,000	$ 5,297	$ 226,563
FY97	451	19891	$ 97,846,089	$ 4,919	$ 216,954
FY98	446	20662	$ 102,547,000	$ 4,963	$ 229,926
FY99	415	20780	$ 128,883,848	$ 6,202	$ 310,563

Source: National Cancer Institute

Forrester Research

Forrester Research estimated the cost of Phase II and Phase III paper and web based (Electronic Data Collection) trials, assuming 200 sites each with 20 patents, as follows:

Table RND 2.8-2: Forrester Research Estimate of Phase II and III per patient costs, with paper and electronic data collection.

	20 sites, 10 patients per site 12 month trials plus data cleaning		200 sites, 10 patients per site 24 month trial plus data cleaning	
	Phase II, paper	Phase II, EDC	Phase III, paper	Phase III, EDC
Average cost per patient	$3,660	$5,672	$5.718	$5,342

Data Edge: Average costs exclusive of central laboratory costs

According to Data Edge, the average costs of all Phase I, II and III trials, exclusive of central laboratory costs, is $4,500 per patent.[15]

Data Edge/ CenterWatch: Average fully loaded costs per patient

The fully loaded per patient (inflation adjusted) costs for clinical trials, from 1992 to 2000, was estimated by DataEdge and CenterWatch as follows

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[15] *Parexel Pharmaceutical R&D Statistical Sourcebook 2002, page 128.*

Table RND 2.8-3: Fully Loaded Costs Per Patient, Phase I, II and III, across all therapeutic areas, 1992-2000.

1992	1994	1996	1998	2000
$ 5,326	$ 5,446	$ 5,873	$ 6,183	$ 6,412

Source: Parexel Pharmaceutical R&D Statistical Sourcebook 2002, page 138.

    Mark Hovde, DataEdge: Mean Costs by Phase

In 1999 Mark Hovde of DataEdge presented the following estimates of the mean costs of clinical studies by Phase.

Table RND 2.8-4: Mean Study Costs by Phase

Phase I	Phase II	Phase III	Phase IV
$9,682	$8,105	$5,465	$3,414

Source: The Research Roundtable: "DataEdge, the King of Research Statistics, Knows How Much You Charge for Research Studies," Vol. 1, No. 5, September 1999

    Per Patient Phase III Costs in Europe, Eastern Europe and South Africa

DataEdge provided estimates of the relative Phase III costs in six Western and Eastern European countries. Using the CenterWatch/DataEdge estimate 1999 for the US cost of Phase III trials at $5,465 as the base case, the costs of Phase III trials is estimated as follows:

Table RND 2.8-5: Cost of Phase III trials in the US and Six Eastern and Western European Countries and RSA

Country	Cost of outsourced Phase III trials
USA	$ 5,465
UK	$ 3,826
Germany	$ 2,842
Poland	$ 2,186
Czech Republic	$ 2,186
France	$ 1,803
Hungary	$ 1,640
South Africa	~$1,800

Source: *The Monitor: Applied Clinical Trials, Vol. 9, No. 7., Reported in Parexel Pharmaceutical R&D Statistical Sourcebook 2002, page 106.*

2.9   Comparisons of Cost Estimates for New Drug Development

Table RND 2.9-1 out of Pocket Costs of Clinical Trials Compared
(Millions of USD)

Study	Phase I	Phase II	Phase III	Total
Tufts	$ 15.2	$ 23.5	$ 86.3	$ 125
PERI	$ 7.3	$ 18.9	$ 43.3	$ 69.5
TB Alliance (Developed Economy)				$ 26.6
TB Alliance (Developing Economy)				$ 9.9

Table RND 2.9-2 Risk Adjusted Cost of Clinical Trials Compared
(Millions of USD)

Tufts	$ 282 million
US Orphan Drug Tax Credit	
Pre-Orphan Drug Credit	$ 11 to $ 34 million
Net of Orphan Drug Credit	$ 5.5 to $ 11million

Table RND 2.9-3 Average Per Patient Cost of Clinical Trials Compared
(Millions of USD)

Tufts	$ 23,572
TB Alliance	$ 644 to $22,000
Robert Kramer, BMS Oncology products	$ 10,000
NIH DCP Cooperative Group Treatment Trials (fy 1999)	$ 6,202
Forrester Research (US)	
(Phase II, paper data collection)	$ 3,660
(Phase II, Electronic data collection)	$ 5,672
(Phase III, paper data collection)	$ 5,718
(Phase III, Electronic data collection)	$ 5,342
DataEdge: US average costs exclusive of central laboratory costs	$ 4,500
CenterWatch/DataEdge: US Fully Loaded Costs Per Patient, Phase I, II and III, across all therapeutic areas (2000)	$ 6,412
Mark Hovde, Data Edge: US Mean Costs by Phase (1999)	
Phase I	$ 9,682
Phase II	$ 8,105
Phase III	$ 5,465
Phase IV	$ 3,414
Phase III trials in the US, Eastern and Western European Countries, and RSA based upon DataEdge indices:	
US	$ 5,465
UK	$ 3,826
Germany	$ 2,842
Poland	$ 2,186
Czech Republic	$ 2,186
France	$ 1,803
Hungary	$ 1,640
South Africa	~$ 1,800

3. Aggregate PhRMA and US IRS data on R&D Outlays

Data on overall expenditures on pharmaceutical R&D are reported from two comprehensive sources, a survey from PhRMA, the leading industry association, and reports from the U.S. Internal Revenue Service.

PhRMA is the US trade association for the largest research-based pharmaceutical companies. PhRMA publishes an annual survey of research and development activities by its members.[16] This survey is widely quoted as evidence of the high rates of industry investment in R&D. Separately, the US Internal Revenue Service (IRS) offers a tax credit for increasing R&D investments. The IRS credit only applies to R&D on new products. There is a significant delay in the availability of information from the IRS. Data for 1998 and 1999, the two most recent years for

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[16] Pharmaceutical Research and Manufacturers of America (PhRMA), *Pharmaceutical Industry Profile 2003* (Washington, DC: PhRMA, 2003)

which we have comparable data, are presented below. First, Table RND-3.0-1 presents the PhRMA numbers for domestic and foreign R&D, global R&D as a percentage of global sales, and global R&D on development of new products. This is followed by Table RND 3.0-2, which reports the IRS figures for global sales and domestic R&D for new products, for the pharmaceutical sector.[17]

Table RND 3.0-1: PhRMA Annual Survey of Member R&D Activities

		1998	1999
R&D	US	$ 17.13	$ 18.47
	Non-US	$ 3.84	$ 4.22
	Total	$ 20.97	$ 22.69
Global R&D as percent of global sales (PhRMA Survey, Table 2)		16.8%	15.5%
Percent R&D for development of new products		80.9%	77.8%
Domestic R&D on new products		$ 13.86	$ 14.37
Global R&D on new products (global)		$16.96	$17.65
Global R&D on new products as percent of global sales		13.6%	12.1%

Table RND 3.0-2: US IRS Data on R&D investments in new products
(Billions of US dollars)

	1998	1999
Sales (includes sales of US firms plus sales associated with US subsidiaries of foreign firms)	$ 189.61	$ 201.29
Domestic R&D on development of new products	$ 12.46	$ 14.81
Domestic R&D on development of new products as percent of IRS sales	6.6%	7.4%
Domestic plus foreign R&D (assuming PhRMA ratio of US to domestic R&D)	$15.25	$18.19
Adjusted rate of investment in R&D in new products (domestic plus foreign R&D divided by IRS sales)	8.0%	9.0%

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[17] The IRS figures include sales from US companies plus foreign corporations with income "effectively connected" with a U.S. business filing.

Figure RND 3.0-1: Product Sales and R&D Expenditures on New Products Reported to US IRS

billions of US dollars
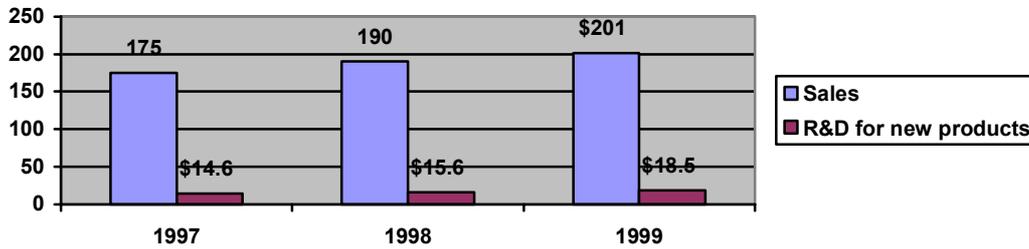
According to earlier PhRMA reports, the share of member company R&D investments devoted to new products was 80.9 percent in 1998 and 77.8 percent in 1999.[18] PhRMA members represent the most important (but not the only) firms conducting R&D. The PhRMA membership survey reports domestic R&D on the development of new products at $13.9 and $14.4 billion, while the IRS reports pharmaceutical R&D investments in new products at $12.5 and $14.8 billion. Based upon the PhRMA data, the rate of investment in the development of new products by its members was 12 to 13.5 percent for the 1998 to 1999 period. The IRS data, which includes the entire pharmaceutical manufacturing sector, places the rate of investment in new products at 8 to 9 percent of turnover for the same period.

The PhRMA member survey says that 32.5 percent of total US domestic R&D investment is spent on pre-human/pre-clinical research and 42.4 percent is spent on human-use clinical testing. PhRMA says that 26 percent of dollars devoted to clinical trials are for Phase IV post-approval clinical studies (11 percent of total R&D spending). Omitting the Phase IV expenditures, the PhRMA survey puts the total share of pre-clinical, Phase I, II and III studies at 64 percent of total R&D outlays. An unknown share of this is actually Phase II or III trials that examine new uses for existing products. PhRMA allocates 7.8 percent to the cost of managing regulatory submissions, and 17.4 percent of total R&D spending is uncategorized in the PhRMA survey.[19]

4. Priority and Standard US FDA NCE Approvals

Not all industry R&D is devoted to new products, and not all new products represent advances in terms of therapeutic benefits. Thus, not all of the R&D costs contained in the PhRMA survey or reported by the IRS are expenditures that have the same value to society.

The US Food and Drug Administration (FDA) classifies new drug approvals on as standard or priority approvals. For new drugs, the FDA awards a priority status if:

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[19] TABLE 5, Domestic R&D By Function, Ethical Pharmaceuticals, PhRMA Member Companies: 2001. (PhRMA 2003).

The drug product, if approved, would be a significant improvement compared to marketed products…in the treatment, diagnosis, or prevention of a disease. Improvement can be demonstrated by, for example: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness of a new subpopulation.[20]

For biologic products, the FDA has a higher standard. A priority review is only awarded when there is evidence of a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a *serious or life-threatening* disease. Table RND-4.0-1 reports the number of FDA-approved NMEs from 1993 to 2002 that were classified as priority or standard reviews. For the 10-year period, 31 percent of NMEs were classified as priority, and 69 percent were classified as standard. Thus, according to the FDA, 69 percent of all new products did not provide evidence that they were significantly better than existing therapies.

Table RND 4.0-1: Priority and Standard NMEs For Calendar Years 1993-2002

Year	Priority	Standard
1993	13	12
1994	13	9
1995	9	19
1996	18	35
1997	9	30
1998	16	14
1999	19	16
2000	9	18
2001	7	17
2002	7	10
Total	79	180
Percent	31%	69%

Using FDA approval letters, Michael Palmedo compared the number of patients in clinical trials cited by the FDA, for 2000-2002 NMEs. According to the Palmedo analysis, for all trials, the average number of patients cited by the FDA was 2,253, and the median was 1,428. For *standard* reviews, the average was 2,667 and the median was 2,238. For *priority* reviews, the average was 1,461, and the median was 905. The number of patients cited in the FDA approval letters are significantly lower than the 5,303 average from the Tufts sample. Part of the disparity is likely due to under reporting of trials on FDA approval letters, and part may be due to a sample selection issue with the Tufts study, which deliberately sought to include large

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[20] Center For Drug Evaluation And Research, MANUAL OF POLICIES AND PROCEDURES (MAPP) 6020.3

projects. However, this would not affect the relative size of trials, when comparing priority to standard reviews. The coefficients of variation are also higher in the Palmedo analysis than in the Tufts study, which is consistent with the notion that the Tufts study omitted smaller trials.

Table RND 4.0-2: Number of patients in clinical, Trials cited in FDA approval letters for NCEs, 2000 - 2002

	Priority	Standard	All
Average	1,461	2,667	2,253
Median	905	2,238	1,428
Standard Deviation	1,826	2,108	2,083
Coefficient of Variation	1.25	.79	.92

Source: Michael Palmedo, 2003

Assuming that the relative number of patients cited in the priority approvals is indicative of the relative investment in priority products, one can estimate the share of investment in new products spent to develop products that are significantly better than existing therapies. Using the 31/69 ratio of priority to standard reviews and the 1,461/2,667 ratio of patients in trials, the share of investments in new products that have significant improvements over existing treatments is 20 percent, with 80 percent of the investment in new products spent on projects that demonstrate no significant improvement over marketed products.

Table RND 4.0-3: Percent of Turnover Invested in Standard and Priority New Products

	All new products	Standard new products	Priority new products
PhRMA (1999)	12.1 %	9.7 %	2.4 %
IRS (1999)	9.0 %	7.2 %	1.8 %
Pharma (average investment in new products, 1993-2002)	13.0 %	10.4 %	2.6 %

The data from the PhRMA survey is presented in Figure RND 4.0-1 below.

Figure RND 4.0-1: Most Private R&D Invested in Products with No Significant Benefits Over Existing Treatments

Sources: Total turnover invested in R&D and share on new producdts from PhRMA membership survey. US FDA approval data on "priority" and "standard" products

New, but not significantly better
9.6%

Research on existing products
4.0%

2.4%

New products rated significantly better than existing treatments
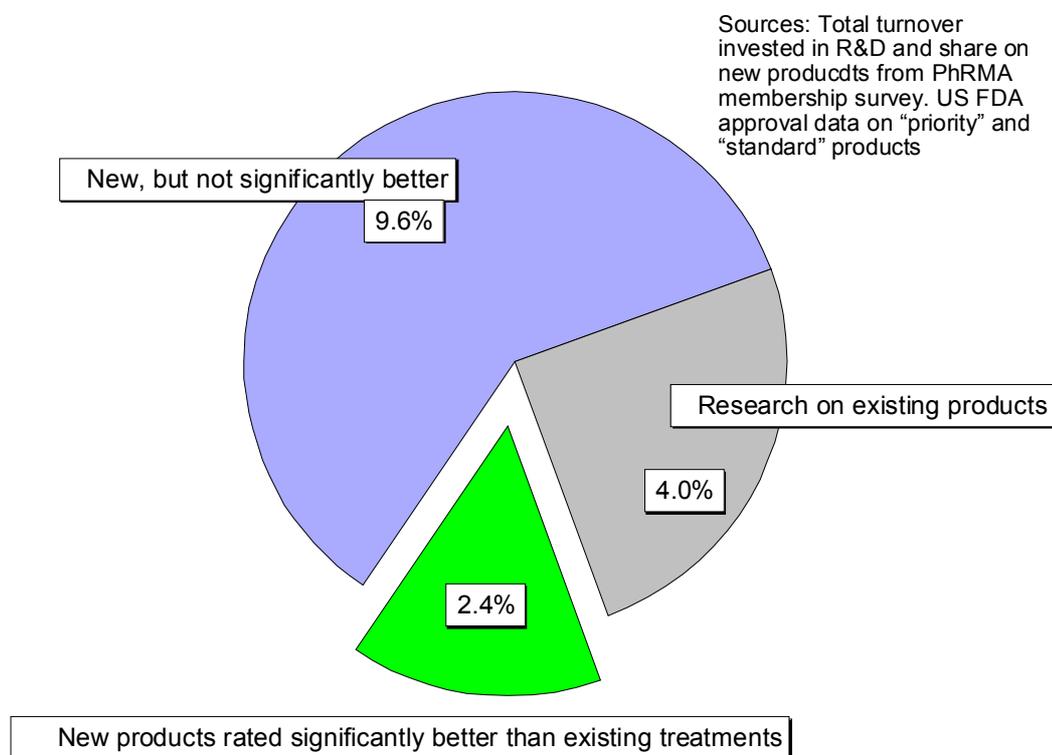
Dr. Joel Lexchin, an expert on marketing practices and the evaluation of new medicines, notes that an independent French drug bulletin places the number of truly innovative products as much lower than does the FDA.

> The French drug bulletin, *Prescrire International*, has recently published summary statistics on almost 2,500 new preparations or new indications for existing drugs that it evaluated between 1981 and 2001. In that time period, it rated just 76 (3.0%) as major or important therapeutic gains while close to 1,600 were assessed as being superfluous because they did not add to the clinical possibilities offered by previously available products.[21]

5. Factors which drive the costs of R&D

The R&D process is complex and many factors are important in shaping costs. Certainly one core factor that drives costs is the demand for research. The greater the commercial rewards for the development of new products, the greater the commercial incentive to invest in R&D. Firms will spend more on individual development projects if the prices and demand are higher. This creates a situation where higher product prices encourage firms to spend more on R&D, and the higher R&D costs one

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[21] Statement of Joel Lexchin, August 2003, citing data from "Drugs in 2001: a number of ruses unveiled," *Prescrire International*, 11 (2002), 58-60.

observes are then used to justify the higher prices, creating a spiral of justifications and incentives that can take on a life of their own.

While it is generally true that the greater the financial incentives, the greater the private sector investment in R&D, there are other very important non-financial factors that influence innovation. The primary barriers to the development of new drugs are cogitative. Clearly a "cure" for HIV would be worth billions, as would more effective treatments for cancer, diabetes, and other severe illnesses diseases. Despite enormous sums invested to combat cancer, it is still a deadly disease, and we do not appear to be close to obtaining a vaccine or cure for HIV -- only treatments that will control or manage the consequences of infection.

Often the key cogitative breakthroughs are not the product of massive private investments, but rather the work of creative academic or government researchers who have the talent to understand the science and a sufficient amount of hard work and luck to make a breakthrough. Recently, there has been renewed interest in the importance of shared information in the development process. New "open medicine" models, such as the government-and donor-funded Human Genome Project or the corporate-funded SNPs Consortium, seek to give all academic and industry researchers access to research tools and data, so that decentralized and collaborative research projects can apply different approaches and insights to different problems.[22] Sir John Sulston, a key figure in the Human Genome Project and the winner of the 2002 Nobel Prize for Medicine or Physiology, recently told researchers that he reckoned open research was nine times as productive as proprietary research.[23] Dr. Harold Varmus, also a Nobel laureate and a former director of the US National Institutes of Health, recently created the Public Library of Science and has become a leader in the Open Journals movement, designed to widen access to scientific information, particularly among researchers in developing countries that have the talent, but often lack access to quality medical research information.[24]

There is also good reason to believe that many of the expenditures are wasteful or designed to meet marketing rather than genuine scientific or public health objectives. In determining appropriate rewards to patent holders for their socially valuable contribution in R&D, it is appropriate to consider the extent to which actual expenditures on R&D address public health needs.

5.1 Pharmacoeconomic Analysis in Clinical Research

When commercial interests perform research, the research program is influenced in many ways, including areas where marketing objectives influence the choice and design of studies. There exists considerable confusion and some controversy over the actual cost of performing clinical trials; but there is general agreement that spending on clinical trials has increased sharply in the past fifteen years. In their study of 1996-

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[22] Declan Butler, "Drive for patent-free innovation gathers pace: Kamil Idris is being asked to assess the merits of an open approach to intellectual property," 118 NATURE, VOL 424, 10 JULY 2003.
[23] Comments made at an April 29, 2003 CPTech, MSF, Oxfam, HAI meeting in Geneva on trade frameworks for funding R&D.
[24] Rick Weiss, "A Fight for Free Access To Medical Research: Online Plan Challenges Publishers' Dominance," *Washington Post*, August 5, 2003.

1998 new drug approvals, Tufts researchers Kaitin and Healy described the underlying reasons for the increases in the costs for pre-approval trials as follows:

> Advances in scientific knowledge, the greater complexity of new products, an increase in the number of pharmacoeconomic studies done in the pre-market phase, and industry inefficiency are contributing to an escalation in the size and complexity of clinical trials, and an increase in research and development costs.[25]

While the first two factors are generally considered positive developments, there is considerable controversy over the benefits of designing trials to address pharmacoecononic and marketing issues. Fred Hassan, then CEO of Pharmacia and PhRMA chair, told *McKinsey Quarterly*,"You're also dealing with demands for very expensive outcome trials from various regulators as well as from managed-care administrators.[26] In a brochure, *Demonstrating Product Potential for Competitive Advantage*,[27] consultant Abt Associates describes the relationship between marketing and science as follows:

> We understand that the transition from clinical development to marketplace introduction is critical to the success of any pharmaceutical, biotechnology, or medical device product. Our expertise can enhance your plans for research before, during, and after market launch. Our projects — which range from small-scale retrospective studies to large-scale prospective registries — can be used to generate greater understanding of the use and value of a new drug, biologic, or device. This understanding in turn supports its use by physicians and managed care organizations (MCOs) as well as appropriate coverage of reimbursement decisions by payors — both public and private. Abt Associates' skill and experience in post-marketing evaluations can help sponsors meet the needs of their marketing and sales teams. Since the 1970s, Abt Associates has conducted hundreds of prospective observational studies and longitudinal surveys to determine the value of healthcare products and services across a wide range of therapeutic areas. We will work with you to achieve the scientific credibility needed to maximize your product exposure.

An undetermined amount of investment in clinical trials, both before and after product approval, is related to marketing issues.[28] Consider these quotes from a *Wall Street Journal* article on clinical trials:[29]

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[25] Kaitin Healy, page 2.

[26] Catherine George and J. Michael Pearson, "Riding the pharma roller coaster," *The McKinsey Quarterly*, 2002 Number 4.

[27] http://www.abtassoc.com/Page.cfm?PageID=6300, Demonstrating Product Potential for Competitive Advantage.

[28] For recent examples of studies designed to achieve marketing purposes, see: http://www.biospace.com/news_category.cfm?CategoryID=25&SR=1

[29] Robert Langreth, "Drug Marketing Drives Many Clinical Trials," *Wall Street Journal,* November 16, 1998.

. . .increasingly, marketing executives are joining research teams from the start, surveying doctors and consumers and tailoring trials to win optimal "positioning" in the marketplace. Many of the biggest trials come not in difficult-to-treat diseases such as cancer, as one might expect, but in well-established therapeutic areas, such as antibiotics or blood-pressure drugs, where enormous testing programs are needed to ferret out small advantages over existing drugs that can then be highlighted in marketing campaigns.

"The FDA told us that we don't need all these trials" to get omapatrilat approved for blood pressure, says Hubert Pouleur, Bristol-Myers's vice president for cardiovascular clinical research. "But there is a difference between getting a drug approved and having it be a commercial success. A new drug will be used only if it is a significant improvement on existing drugs, and to establish that you need trials that aren't required for approval."

Postmarketing studies, as trials for drugs already on the market are called, "are billowing out of control," says Eve Slater, Merck's senior vice president for clinical testing. She decries "a total lack of science" in some studies. But drug marketers contend they are helpless to stop the one-upmanship. If a rival mounts a new study aimed at backing up a sales-expanding marketing claim, "you have to do it, too, or you are dead in the water," she says.

Seeding Studies

A particularly controversial mixture between research and marketing are so-called "seeding studies," which are designed to promote the use of medicines. [30]

Traditionally, once a product has been launched the company wants to gain as much market share as possible to gain return on investment. One way of achieving the involvement of prescribers and patients is the use of 'seeding' studies. In such trials, the data is often collected by sales reps rather than Contract Research Organizations (CRAs) and patient recruitment is often thinly spread over a large number of sites.[31] Seeding studies are generally held in very low esteem, particularly if the company attempts to masquerade them as Phase IV studies. Some of the characteristics of seeding studies are listed below:

Characteristics of Seeding Studies

- Lack of control group
- Inadequate statistical power

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[30] La Puma J. Physician rewards for postmarketing surveillance (seeding studies) in the US. Pharmacoeconomics 1995;7(3):187-90. Steven Piantadosi, *Clinical Trials: A Methodologic Perspective*, John Wiley and Sons, New York, 1997.
[31] http://www.pmlive.com/archive.cfm?&ArticleID=175&back=-1&print=1, Clinical Trials: Part Two: Marketing and Clinical Trials.

- Involvement of a large number of study sites, each recruiting only a few patients
- Inappropriate use of sales representatives
- Vague safety aim, irrelevant or inappropriate outcomes
- Short-term studies with a drug intended for long-term use
- Paid for directly by the company's marketing department

One interesting analysis of the role of seeding studies in marketing was recently published in The Netherlands by the Health Care Inspectorate.[32] The 25-page report details a wide range of areas where research and marketing are blended together, often apparently in violation of Dutch and European regulations on ethical marketing practices. Of particular interest here are some of the discussions of the practice of using clinical trials as marketing practices.

> Expenditure on combined scientific and marketing studies are sometimes included under expenditure for research and development and clinical studies and not in the marketing plans.. . . All studies (including Phase IV studies) must meet the criteria set out in the Medical Research Involving Human Subject Act. These tests must be checked by a medical ethics committee. Exposing people to non-scientific studies using medicinal products is unethical.

> *Findings*

> In some cases the marketing plans refer to designations which fall under the phase IV study, such as value-added projects, post marketing surveillance (PMS), **seeding trials**, phase IV study, clinical trial and study. . . The objectives of the phase IV studies described in the plans show that influencing prescriptions for the product being promoted and building up relationships with the doctor are mentioned in 48 of the 71 surveys (68%). There are no specific study objectives in the remaining 23 surveys. In addition to money, incentives in kind offered to doctors including sphygmomanometers, hand-held computers etc. are mentioned... The designations in the studies suggest that they could be described as scientific studies. The fact that no specific study objectives were mentioned in some of the studies leads us to assume that the execution of the study is not a prime objective. The question is how the medical-ethics committees have interpreted their tasks in these cases. This is all the more so in those cases in which the marketing plans have explicitly mentioned influencing prescriptions as an objective. Presenting these forms of influencing as research can be seen as socially unacceptable and unethical. It undermines the public's trust in healthcare. The articles in the Medicinal Products Advertising Decree are not legally geared towards tackling this.

Another section of the Dutch Health Care Inspectorate report describes other research-related activity that have marketing objectives.

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[32] Health Care Inspectorate, Marketing plans for medicinal products available on prescription only: the current situation, The Hague, July 2001, second revised edition.

Investigations by the Inspectorate have revealed that about 50% of refresher courses for GPs are sponsored and/or organised by the pharmaceutical industry. The pharmaceutical industry often determines who is invited, thus creating restricted access for the profession as a whole. Because the topics are generally determined by the pharmaceutical industry, the course programmes are more likely to be supply-oriented rather than demand-oriented. The question is whether the needs of public health are served by this situation. About NLG 18,000,000, or about 11% of the total [marketing] budget, is spent on promotional meetings which are often not accredited. These meetings are made attractive to the target group by linking them to attractive locations and/or events. The objectives mentioned in the plans include persuading doctors that the medicinal product in question is the best, increasing the number of patients treated, and encouraging or influencing doctors to participate in phase IV studies.

5.2 Conflicts of Interest

Another difficult-to-quantify inefficiency from clinical trials concerns the problem of conflicts of interest, an issue deemed so serious by some that there are proposals to fundamentally restructure the mechanisms under which clinical trials are funded.[33]

5.3 Haste Makes Waste? / Recruiting Patients

Firms are sometimes under tremendous pressure to speed the completion of clinical trials, as described in this consultant's report:[34]

Delays can cost pharma companies at least $800,000 a day in lost sales for a niche medication, such as Amaryl, an oral antidiabetic treatment, and as much as $5.4 million for a blockbuster like Prilosec, a gastrointestinal medication. If some of this revenue is merely deferred, it may be recouped once a drug goes on the market, but millions of dollars in revenue can vanish if a competitor catches up or, worse, gains the advantage with an earlier debut. Delays can also affect a company's valuation, since investors closely watch the progress of new drugs: efficient clinical trials put them on the market more quickly, so

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[33] Richard Smith, "Medical journals and pharmaceutical companies: uneasy bedfellows, *BMJ* 2003;326:1202-1205 (31 May); John La Puma, Carol B Stocking, William D Rhoades, Cheryl M Darling, "An Ethical Debate: Financial ties as part of informed consent to postmarketing research, Attitudes of American doctors and patient," *BMJ* 1995;310:1660-1661 (24 June); Evans RG: Manufacturing consensus, marketing truth: guidelines for economic evaluation. Ann Intern Med; 1995; 123(1):59-60; Davidson RA: Source of funding and outcome of clinical trials. J Gen Intern Med 1986, 1: 155-158; Schulman KA, Rubestein LE, Glick HA, et al: Relationships between sponsors and investigators in pharmacoeconomics and clinical research. Pharmacoeconomics;1995; 7(3):206-220; Relman AS: Dealing with conflict of interest. N Engl J Med; 1984; 310:1182-1183; Drummond MF: Economic evaluation of pharmaceuticals: science or marketing? Pharmacoeconomics; 1992, 1(1): 1-13; Friedberg M, Saffran B, Stinson TJ, et al: Evaluation of conflict of interest in economic analyses of new drugs used in oncology. JAMA; 1999; 282(15):1453-1457; Krimsky S: Conflict of Interest and cost-effectiveness analysis. JAMA; 1999; 282(15):1474-1475.

[34] Janice Cruz Rowe, Martin E. Elling, Judith G. Hazlewood, and Randa Zakhary, "A Cure for Clinical Trials," *The McKinsey Quarterly*, 2002 Number 2.

they take market share more quickly. Pharma companies may also
gain a strategic edge by setting a new standard for treating a disease,
and speed to market gives physicians and patients a broader, and
potentially lifesaving, choice of treatments in less time.

In order to speed up trials on perceived commercially important products, firms will
pay dearly. One former company executive reported that firms sometimes spend huge
sums to shave months off a trial completion. One of the key bottlenecks in trials is
the recruitment of patients. There is now a growing industry of firms that specialize
in patient recruitment. Consider for example this quote from a Mathews Group
brochure.[35]

> *Taking the Guesswork out of Patient Recruitment.*
> What's a better recruitment tool, TV or radio? How many calls will it
> take to yield a patient on a study? What's the per-patient cost to fill a
> trial? What regulatory or institutional review board requirements
> should be considered? These are questions clinical investigators and
> study coordinators ask—and MMG can answer. MMG designs patient
> recruitment strategies to help clients find the participants they need for
> clinical studies—strategies customized to therapeutic area, target
> audience demographics, and eligibility. We base each tactic on
> outcome data from our extensive database of results from previous
> trials and on statistics derived from MMG's call center, study sites,
> media tracking, and research. MMG messages reach diverse
> populations including children, older adults, non-English speakers, and
> racial and ethnic minorities. We disseminate brochures, posters, and
> other recruitment materials wherever people look for information—on
> the Internet, at doctors' offices, at pharmacies, in support groups, and
> more. We run intensified television, radio, and print advertisements in
> key markets, and place news stories in publications where participants
> are most likely to see them. With reliable metrics, we take the
> guesswork out of the patient recruitment process.

Another important mechanism to speed patient recruitment is to pay patients to
participate, or to pay bounties to the doctors or other health care workers who recruit
patients. This practice is described by Dr. Marcia Angell, a former editor of the *New
England Journal of Medicine*, in a recent NIH publication.

> Because of the way patent law works, companies regard time spent
> conducting trials as a delay in bringing new drugs to market, so they
> are hasty and indiscriminate when recruiting patients, Angell said. . . .
> Companies pay bounties of anywhere from $500 to $15,000 per
> subject ("more than enough to cover costs") to load their trials, plus
> bonuses for rapid enrollment.[36]

The difficulty of recruiting patients increases when the benefits of being a test subject
are small, and when the risks are large or uncertain. It is much easier to recruit

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[35] http://www.matthewsgroup.com/brochure.pdf.
[36] Richard McManus, "Abolitionist' Angell Calls for Clinical Trial Reform," *the NIH Record*, July 24,
2001, Vol. LIII, No. 15.

patients for promising product for a severe illness that has no satisfactory treatment than it is for a "me too" product that is unlikely to be significantly better than existing therapies that has risks of adverse side affects.

6. HIV products

As noted earlier, there are significant differences in the variables that determine the private cost of developing products. These include such factors as the duration and size of trials, the time and regulatory burden of FDA review, and the role of government funding for pre-clinical or clinical research, both directly and indirectly via tax credits. In virtually every area, HIV products have had characteristics that lower their development costs. The size of clinical trials used for FDA approval have been relatively modest, and the trials themselves are both short and relatively inexpensive to administer, with few problems recruiting patients. FDA approval times have been short, and most HIV products benefited from abbreviated procedures. A large number of HIV products have benefited from significant US government subsidies, including every product in the current case.

6.1 Duration of HIV Trials

The Kaitin and Healy study of 1996-1998 US FDA new drugs approvals[37] examined mean clinical and approval times for eight therapeutic classes of drugs. AIDS antiretroviral drugs had the shortest clinical phase *and* the shortest FDA approval times. For all products, the average duration for the clinical phase was 70.3 months -- 5.9 years. For ARV products, the average clinical phase was 40.1 months -- 3.3 years. For all products, the average FDA approval period was 16.3 months. For ARV products the average approval period was just 4.6 months.

Table RND 6.1-1: Mean clinical and approval phase times for NCEs approved 1996 to 1998, grouped by therapeutic class

	Clinical Phase	Approval Phase	Total
Endocrine (n=9)	96.1	10.6	106.7
Neuropharmacologic (n=15)	87.5	19.2	106.7
Andneplastic (n=11)	80.9	16.2	97.1
Cardiovascular (n=25)	69.2	18.3	87.5
Respiratory (n=7)	65.6	26.4	92.0
Antiinfective (n=13)	63.3	16.3	79.6
Anesthetic/Analgesic (n=9)	57.9	17.7	75.6
AIDS antiretrovials (n=9)	40.1	4.6	44.7
Average (n=110)	70.3	16.3	86.6

Source: Kaitin and Healy (2000), CSDD

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[37] Kenneth I. Kaitin and Elaine M. Healy, "The New Drug Approvals of 1996, 1997, and 1998; Drug Development Trends in the User Fee Era," *Drug Information Journal*, Vol. 34, pp. 1-14, 2000.

6.2 Researcher Letter to *New York Times* Regarding Role of US government in supporting R&D for AZT

The role of the US government in supporting the development of AZT was spelled out in this September 28, 1989 letter from five government or government-funded researchers.

New York Times, September 28, 1989
Credit Government Scientists With Developing Anti-AIDS Drug
To the Editor:

The Sept. 16 letter from T.E. Haigler Jr., president of the Burroughs Wellcome Company, was astonishing in both substance and tone. Mr. Haigler asserts that azidothymidine, or AZT, was essentially discovered and developed entirely by Burroughs Wellcome with no substantive role from Government scientists and Government-supported research. This will be a surprise to the many men and women who have devoted their lives to working for the viral cancer program and developmental therapeutics program of the National Institutes of Health over the last 25 years.

We (associated with the National Cancer Institute and Duke University) make this statement as co-authors of the first publications describing AZT as a drug for treatment of acquired immune deficiency syndrome (Mitsuya, et al., Proceedings of the National Academy of Sciences, 1985, and Yarchoan, et al., The Lancet, 1986). There are few drugs now approved in this country that owe more to Government-sponsored research. In the interest of brevity, perhaps this point can be summarized most efficiently by stating what Mr. Haigler's company did not do.

*   The company did not perform the first synthesis of AZT. This was done by Dr. Jerome Horowitz at the Michigan Cancer Foundation in 1964, using a Government grant.

*   The company did not conceive or provide the first demonstration of an effect against animal retroviruses. This was done by Wolfram Ostertag at the Max Planck Institute in 1974, using a mouse retrovirus in a test tube. Mr. Haigler's implication that his staff "discovered" the antiretroviral potential of AZT in 1984 is noteworthy. What he did not say was that his staff repeated the Ostertag mouse experiments. You cannot discover" something published by someone else 10 years earlier.

*   The company specifically did not develop or provide the first application of the technology for determining whether a drug like AZT can suppress live AIDS virus in human cells, nor did it develop the technology to determine at what concentration such an effect might be achieved in humans. Moreover, it was not first to administer AZT to a

human being with AIDS, nor did it perform the first clinical pharmacology studies in patients. It also did not perform the immunological and virological studies necessary to infer that the drug might work, and was therefore worth pursuing in further studies.

All of these were accomplished by the staff of the National Cancer Institute working with staff at Duke University. These scientists did not work for the Burroughs Wellcome Company. They were doing investigator-initiated research, which required resources and reprogramming from other important projects, in response to a public health emergency. Indeed, one of the key obstacles to the development of AZT was that Burroughs Wellcome did not work with live AIDS virus nor wish to receive samples from AIDS patients.

In a number of specific ways, Government scientists made it possible to take a drug in the public domain with no medical use and make it a practical reality as a new therapy for AIDS. It is unlikely that any drug company could have found a better partner than the Government in developing a new product. We believe that the development of this drug in a record two years, start to finish, would have been impossible without the substantive commitment of Government scientists and Government technology. It does not serve anyone's interests to nullify the importance of Government-sponsored research in solving problems of American public health.

HIROAKI MITSUYA, M.D.
KENT WEINHOLD
ROBERT YARCHOAN, M.D.
DANI BOLOGNESI
SAMUEL BRODER, M.D.
Bethesda, Md., Sept. 20, 1989

Burroughs Wellcome also benefited from the US Orphan Drug Act, which provided a credit of 50 percent of the private outlays on clinical trials.

6.3 Expanded Access Programs

For some severe illnesses, including HIV infection, firms will make products available in "expanded access" programs, while FDA marketing approval is pending. These programs are sometimes structured as clinical trials, but with weak or limited scientific goals, as the trials are primarily designed to promote access to the medicine. There are
similarities between these programs and so called "seeding" trials, discussed above. The company may seek to promote market acceptance of a product prior to official marketing approval, and to build relationships between company marketing representatives and prescribing doctors. Expanded access programs were common for early antiretroviral drugs. **[REDACTED]**
It is generally assumed that such trials are considerably less resource intensive than the critical trials designed to support claims of safety and efficacy.

6.4 Key facts about the particular NMEs in this case:

AZT

> Compound invented on US government grant in 1964
> Designated Orphan Drug for treatment of HIV on July 17, 1985
> Extensive involvement with NIH/NCI on development of drug.[38]
> BW/GSK key use patent filed 17 September 1985.
> FDA approval filed December 2, 1986 / granted March 19, 1987
> Duration of regulatory approval period - 3.5 months
> Number of patients cited in FDA approval letter - one trial / 282 patients
> Median analysis time in clinical trials - 18 weeks
> Time from patent filing to FDA approval - 6 months

3TC

> Compound invented by BioChem Pharma
> Key patent filed 8 February 1989
> NIH funded 14 studies of use of 3TC to treat AIDS and Hepatitis
>   through 1995
> FDA approval filed June 30, 1995 / granted November 17, 1995
> Duration of regulatory approval period - 4.5 months
> Clinical trials cited in FDA approval letter - four trials / 982 patients
> Analysis time in trials - 24 weeks
> Time from patent filing to FDA approval - 6 years, 9 months, 14 days
> GSK reported a large

Nevirapine

> Compound invented by Boehringer Ingelheim
> Key patent filed 13 July 1993
> From 1993 to 1996 NIH funded 40 studies of Nevirapine
> FDA approval filed 23 February 1996 / granted June 21, 1996
> Duration of regulatory approval period - 4 months
> Clinical trials cited in FDA approval letter - 2 trials / 549 patients
> US government sponsored largest trial of 398 patients
> Analysis time in trials - BI trial was 76 weeks, US government trial
>   was 48 weeks
> Time from patent filing to FDA approval - 2 years, 11 months, 9 days

Each of these three products had a modest number of patients in trials for a relatively short duration, and benefited from US government funded research.

7. Choice of Mechanisms to support R&D

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[38] See letter above from NIH/Duke researchers to *NYT*.

The patent system is a particular mechanism to fund R&D on new products, but it is by no means the only one, as evident from the plethora of public sector efforts to support R&D. There are a number of reasons why private sector R&D efforts are routinely supplemented by direct and indirect public sector investments in R&D.

7.1 Insufficient R&D for diseases the primarily afflict the poor

In a recent report for a World Bank meeting on pharmaceuticals, Love and Hubbard noted the areas where private incentives from patents lead to too little R&D investment for diseases that primarily afflict the poor.[39]

> It is widely acknowledged that there is too little investment in R&D for diseases that primarily afflict the poor. R&D for "neglected diseases" is appallingly low, given the suffering and death that is involved. According to one study, of the 1,393 new drugs approved between 1975 and 1999, only 16 (just over 1%) were specifically developed for tropical diseases and tuberculosis, diseases that account for 11.4% of the global disease burden.[40] This market failure is explored in detail every year in the Global Forum for Health Research's reports on the 10/90 gap, which is described as follows:

>> Every year more than US$70 billion is spent on health research and development by the public and private sectors. An estimated 10% of this is used for research into 90% of the world's health problems. This is what is called "the 10/90 gap".

> Public health groups such as MSF note that the financial incentives that patents are supposed to provide "will not stimulate R&D into neglected diseases such as Chagas' diseases, kala azar, and sleeping sickness precisely because the people who suffer from neglected diseases do not have substantive purchasing power, and do not constitute a profitable market."[41] In looking toward new tools from genomics, Carlos Morel, who directs search on tropical diseases for the WHO, warns that "if this challenge is left exclusively in the hands of market forces, or addressed by laissez-faire scientific and technological policies, genomics will increase the divide between the rich and the poor, instead of bridging it."[42] That is, market driven investments will

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39 James Love And Tim Hubbard, "An Agenda For Research And Development: Meeting On The Role Of Generics And Local Industry In Attaining The Millennium Development Goals (MDGs) In Pharmaceuticals And Vaccines," The World Bank, Washington DC. June 24-25, 2003.
40 P Trouiller Et Al., Drug Development For Neglected Diseases: A Deficient Market And A Public-Health Failure, Lancet 2002 359:2188-194
41 See For Example, The MSF Testimony At A Members' Briefing On Infectious Diseases In The Developing World: Problems Of Access And Inadequate Research And Development Of Medicines - Hosted Jointly By The Congressional Human Rights Caucus And The Congressional Black Caucus Health Brain Trust, Available At: Http://ww.House.Gov/Lantos/Caucus/Testimonytorrente051403.Htm , The Joint NGO Statement In Response To The US Proposed Resolution On Iprs, Innovation And Public Health At The 56th WHA, And MSF, Fatal Imbalance, The Crisis In Research And Development For Drugs For Neglected Diseases, 2001.
42 Carlos Morel, "Neglected Diseases: Under-Funded Research And Inadequate Health Interventions," EMBO Reports, Vol 4, 2003.

ignore the needs of those who suffer from diseases that primarily afflict the poor.

7.2 The Need to Address Public Health Priorities

Even in cases where a public health problem confronts both the rich and the poor, there are often insufficient investments in new treatments, particularly in the areas of vaccines and other measures to prevent illness, or for risky projects. This is the case even when the health problems or risk are quite important, if they are considered too risky or unprofitable from a commercial point of view. One recent illustration is the SARS outbreak, which has the possibility of becoming a widespread health care crisis, as illustrated in this report from the *Washington Post.*

> While the sudden emergence of SARS, the severe acute respiratory syndrome, is a global health emergency of the highest order, it's not at all clear yet that it represents a commercial opportunity. Scientists are announcing breakneck progress, including isolation and genetic mapping of a new SARS virus, that may, under the right circumstances, lay the groundwork for new treatments. But executives in the pharmaceutical and biotech industries say those treatments won't come automatically or quickly -- and may not be needed at all, if public health experts succeed in controlling the virus through the simpler expedient of quarantine. Only if quarantine fails and the virus becomes widely established in the human population, the executives say, will the numbers of victims rise to the point that it makes sense to launch programs to discover new drugs and vaccines. While many experts fear the virus has already spread too widely to be eradicated, they are not yet certain. Scores of companies are looking at the prospects, but few, so far, appear to be committing large sums to SARS research. "It's only a good commercial opportunity if worst cases are realized," said William A. Haseltine, chairman and chief executive of Human Genome Sciences, Inc.[43]

Public sector funds have been instrumental in research on SARS and bioterrorism, but also in nearly every area where there are important health care problems, including AIDS, cancer, diabetes, asthma and other illnesses. Government supported health care research is used in a variety of ways to support innovation. One is to support the building of a body of general scientific information, published research, and specialized databases and other research inputs.[44] But government supported research can cover every aspect of R&D, including every aspect of drug development. In August 2003, the US National Institutes of Health was recruiting patients for 2,832

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43 Justin Gillis And Michael Barbaro, "SARS No Boon For Drug, Biotech Firms," Washington Post; April 17, 2003.
44 An excellent summary of this is J. H. Reichman and Paul F. Uhlir, "Contractually Reconstructed Research Commons For Scientific: Data In A Highly Protectionist Intellectual Property Environment," LAW AND CONTEMPORARY PROBLEMS, Vol. 66:315.

clinical trials that it sponsors directly, including 293 studies involving HIV.[45] Other US federal agencies are recruiting patients for 186 clinical studies. This is in addition to recruiting for 1,796 studies being carried out by universities, many of these funded by the US federal government. US expenditures on the National Institutes of Health now exceed $27 billion per year.   Europe is seeking to expand its national expenditures on R&D, relying in part on increased public sector expenditures. In the 6th R&D framework program, the number one priority is life sciences, genomics and biotechnology for health and to combat major diseases, which has been allocated €2.2 billion in public sector funds.

Investments in public sector R&D are highly correlated with increased private sector investments in R&D. In data collected by the European Commission,[46] every $1 of public sector investment in R&D is correlated with $2.26 in private sector R&D spending,[47] and in cross national comparisons is a much better predictor of private sector investments in R&D than the domestic intellectual property regime.

7.3 New Models for Funding R&D

As noted above, there is a growing interest in the development of new "open" research models that provide the widest access to scientific information. A very important and well-known example of an open public good research model is the Human Genome Project. As said in an April 14, 2003 joint statement by the heads of state for France, the US, the UK, Germany, Japan and China, "scientists from six countries have completed the essential sequence of three billion base pairs of DNA of the human genome, the molecular instruction book of human life. . . This information is now freely available to the world without constraints via public databases on the World Wide Web." The researchers on the Human Genome Project (HGP) were keen to avoid the patenting of the basic building blocks to scientific research.   A 2000 statement by the WHO Expert
Consultation on New Developments in Human Genetics expressed concerns that "gene patenting could impede international collaboration, especially between developed and developing nations."[48] Stanford Law School Professor, John Barton has expressed the difficulties presented when the patent system creates barriers to research.[49]

> Some of these patents can preempt large areas of medical research and lay down a legal barrier to the development of a broad category of products. The possibility is particularly strong in biotechnology for several reasons: there are so many broadly relevant patents; research builds on the use of so many prior discoveries; and solid and clear title to a product is so important to the pharmaceutical industry. A researcher must therefore sometimes consider either redesigning a

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[45] The NIH Web page clinicaltrials.gov lists another 1,198 trials involving HIV that have been completed.

[46] *Towards a European Research Area: Science, Technology and Innovation, Key Figures 2002*.

[47] Based upon a cross section of 16 OECD countries. The result is statistically significant (p-value < .01).

[48] Statement of the WHO Expert Consultation on New Developments in Human Genetics, WHO/HGN/WG/00.3.

[49] John Barton, "Research-tool patents: issues for health in the developing world," *Bulletin of the World Health Organization* 2002; 80:121-125.

research programme in order to avoid using patented techniques, or expending the effort to obtain licences from the patent holders. The task of assembling all the legal rights necessary to market a product may be so great as to discourage a firm from proceeding. Even if the total licence fees can be kept low, there are enormous negotiation costs, and one ''hold-out'' may be enough to cause the project to be cancelled.

In recent years, there has been an explosion in critical evaluations of the patent system as it applies to software, business methods, Internet protocols, research tools and medicine and biotechnology. These critiques have not only focused on the issues of access or fairness, but also on the core issues of efficiency in fostering innovation, the putative rationales for the patent systems. Some are now calling for new global trade mechanisms to support health care R&D that reconcile both the public health and ethical requirements that inventions be available to the poor with the need to increase investments in the treatments that are most needed to address public health problems. The World Bank is scheduling two meetings on this topic this fall, the World Health Organization will be launching a major review of innovation and public health, and a plethora of expert groups, commissions and studies are focusing on the thorny problems of promoting innovation in the modern world.

8. Evaluation and Conclusion
[REDACTED]

[REDACTED]

The Tufts study is not a useful estimate of the R&D investments in the ARV products in this case, for the following reasons. The projects selected for the Tufts study were not typical of ARV products in terms of the size of clinical trials, time to market, or the role of government in subsidizing R&D. The Tufts estimates of the average per trial and per patient cost of clinical trials was also not representative of other independent evidence concerning drug development costs.

[REDACTED]

GSK's most recent annual report to investors reports that 15.2 percent of turnover is invested in R&D. For BI the figure was 17.2 percent. If GSK and BI follow industry averages in terms of shares of investments between (a) existing products, and new products that are (b) not significantly better or (c) significantly better than existing treatments, the rates of investment in R&D can be presented as follows:

Table RND 8.0-1: GSK and BI reinvestment in R&D for existing products, new products not significantly better than existing treatments, and new products significantly better than existing treatments.

	Self Reported global rate of investment in R&D	Investment in older products	Investments in new products that are not significantly better than existing treatments	Investments in new products that are significantly better than existing treatments
GSK	15.2%	3.8%	9.1%	2.3%
BI	17.2%	4.3%	10.3%	2.6%

Assuming that GSK and BI's reinvestment in R&D is the same for South Africa as it is for other countries, and without making any judgements regarding the efficacy or relevance of the R&D investments for South Africa, the benefits of the GSK and BI investments in R&D from sales of AZT, 3TC, Combivir and Nevirapine, are estimated as follows:

Table RND 8.0-2: Benefits in R&D funded by current sales of GSK and BI antiretroviral products *(in millions of)*

	Sales in ZAR through June 30, 2003	R&D invested in older products	R&D invested in products not significantly better than existing treatments	R&D invested in new significantly better products	Total
GSK	R81.8	R3.1	R9.3	R1.9	R14.3
BI	R19.5	R0.8	R2.5	R0.5	R3.9

To the degree that South Africa seeks to support innovation in health care, it could reasonably target such efforts in areas of the most need in South Africa, and avoid mechanisms that impede access to medicines, or which are economically inefficient.