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How Much does it cost to develop a new drug

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How much does it cost to develop at new drug? In 1988, the National Cancer Institution estimated it spent about $1 million to fund develop of a drug through Phase II trials, and another $1.6 million to $4 million for Phase III trials, for cost of $2.6 to $5 million. From 1983 to 1993, the pharmaceutical industry reported spending $2.3 million on clinical trials for each new FDA approved orphan drug. In 1991, NCI said it was spending more than $30 million on clinical trials for the cancer drug Taxol. In 1999, PhRMA testified that the average cost of drug development was $.5 billion, and that only 1 in 5,000 compounds are successful. Bristol-Myers Squibb now claims that it has spent more than $1 billion to develop Taxol, a drug it did not invent. While the costs of drug development are less of a mystery than one might think, clearly there is considerable confusion about the costs of research and development for a new drug.

These are some of the sources of this confusion.

1. Allowances for Risk and the Opportunity Cost of Capital

Some estimates are based upon the direct costs of drug development, without accounting for the risk of failures, and without adjustments for inflation or the cost of capital. Others include both these items. For example, the US government's investments in Taxol development were reported as the nominal costs of research on Taxol, and did not reflect the costs of government research on other products that were unsuccessful. Nor did the NCI include adjustments for inflation or the opportunity costs of capital. Studies promoted by PhRMA include adjustments for risk and for the opportunity cost of capital -- the latter using very high capital costs.

2. Definitions of "development" vary.

One important question is what does it cost to discover and test a drug, through the point where the drug is approved for marketing. This is how I would normally define the costs of drug development. But the pharmaceutical companies often use a much different definition. For example, when asked how much of its own money it spent to develop Ceredase, a drug invented on NIH grants, Genzyme Corporation included the costs of

building a factory for commercial production. When BMS was asked in 1993 how much it spent on Taxol development, it said more than $114 million dollars. BMS did not invent Taxol, did not sponsor the clinical trials used for the FDA approval, and did not even know how to manufacture the drug. BMS included in its "development" costs the projected costs of a long term supply contract for production of Taxol from Hauser Chemicals (a former NCI contractor), and a long term agreement with a firm to grow Yew trees for Paclitaxel production. In other cases, companies may include such items as the costs of marketing a new drug, an item certainly part of a business plan, but not a research expense. There is also money spent to find new uses for a drug, once it is on the market, and investments in clinical trials that have marketing objectives, such as to justify inclusion of the drug in national or private formularies.

3. Companies take credit for things they do not do.

While in some cases, a company may do all of the important stages of research and development for a drug, including both clinical and pre-clinical investments, but in other cases governments or private donors fund important parts of research. Studies have shown that the government role is particularly true for innovative drugs for severe illnesses, and less significant for so called "me too" drugs, or for drugs such less important public health problems, as hair loss.

When the government funds the discovery of a drug, such as in the case of AIDS drugs like AZT, ddI, ddC, d4T, Ziagen and Norvir, the taxpayers have paid for the most expensive part of the R&D process. In the often quoted 1991 study by Joseph DiMasi and his colleagues, the costs of preclinical expenditures were 67 to 73 percent of the total development costs, depending upon the assumptions regarding the opportunity costs of capital. So when the government is responsible for the pre-clinical discovery, 2/3 to 3/4 of the costs of the drug are already paid for, according to the DiMasi analysis.

This is also true for each stage of the clinical process. For example, d4T was discovered on an NIH grant, and its use for HIV/AIDS was discovered at Yale, on a government grant. Then the NIH was a sponsor of the first Phase I trial on d4T. When companies enter the R&D pipeline at the Phase II or Phase III stage, the are entering at the tail end of a process, avoiding investments, risk and time -- the three critical elements in a cost study.

It is also the case that it is often less expensive to develop the second or third drug within a therapeutic class, than the first, because the risks are less. Once AZT was identified as a product that would treat HIV/AIDS, there was a rush to test other nucleoside analogue reverse transcriptase inhibitors. Similarly, after the first protease inhibitors or non-nucleoside reverse transcriptase inhibitors where shown to be effective for HIV/AIDS, the risks were lowered for the next versions of drugs in these therapeutic classes.

4. Samples can be skewed and average can be misleading

In his 1991 study of the costs of clinical trials, DiMasi indicated that the median costs of clinical trials were about 60 percent of the average costs. DiMasi also reported that the costs of successful trials were considerably higher than the costs of unsuccessful trials, on average, suggesting companies invest more when risks are lower.

In my examination of the US Orphan Drug Tax Credit, the reported industry outlays on clinical trials were only $2.3 million per approved drug, a number adjusted for risk but not opportunity costs. This was a small fraction (after adjustments for inflation, about 6 percent) of the "averages" used in the DiMasi study. There were probably several reasons for the differences, including the fact that the US government had paid for all or part of the costs of clinical trials for many of the orphan drugs. But PhRMA claimed the difference was because orphan drugs were much cheaper, because of the smaller sizes of clinical trials and the fast track regulatory procedure. The category of orphan drugs is larger than one might think, and several "blockbuster" drugs have qualified for orphan status. Indeed, during the period of 1983 to 1993, all HIV/AIDS drugs qualified as orphan drugs. And in 1998, about half of all US FDA approvals for new molecular entities (NME) were classified as orphans.

One can also look at other assumptions in the DiMasi study and see issues regarding averages. DiMasi 1991 study used the following periods for the period between the beginning of a stage of development and the approval of a drug:

Table 1
DiMasi's 1991 estimate of Time to Market

	Start to NDA	Phase Length
Preclinical	11.8	3.6
Phase I	8.2	1.3
Phase II	6.9	2
Phase III	5	3
NDA Review	2.5	2.5

The data on time to market are quite important when one is calculating the opportunity cost of capital, which is in fact, the lion's share of costs in studies by DiMasi, the OTA and others.

When we looked at development times for HIV/AIDS drugs, the DiMasi/OTA assumptions did not seem realistic. For all 14 HIV/AIDS drugs approved by the US FDA (In the class of nucleoside analogue reverse transcriptase inhibitors, protease inhibitors, and non-nucleoside reverse transcriptase inhibitors), the average

time from filing a patent to NDA approval was only 4.4 years. (Table 14) The longest period between filing for a patent and FDA approval was 8 years, for Ziagen, a drug discovered by the University of Minnesota, now sold by Glaxo. The period was much shorter for many drugs, and in particular, the first drugs in a therapeutic class. (See Table 14)

For AZT, the first nucleoside analogue reverse transcriptase inhibitor, the time between filing the patent and product approval was 1.5 years. For protease inhibitors Ritonavir/Norvir and Indinavir/Crixivan the period was .9 and 2.9 years, respectively. For the three non-nucleoside reverse transcriptase inhibitors, the period of 2.9 to 3.3 years.

When asked about AIDS drugs, DiMasi said his own data suggested AIDS drugs were about the same as other drugs in terms of development time. But his averages were based upon data points that could be misleading. For AZT, a drug that was on the market 1.5 years after the patent was filed, DiMasi used the earlier 1964 date of discovery of the compound, for the beginning of preclinical research, giving AZT more than 20 years. The same was done for ddI and other drugs, even though the initial discovery of the compounds were done by government funded researchers.

How important are data on the timing of development? When an estimate of drug development costs includes the opportunity cost of capital, the investments are increased at a compound rate of interest. At 14 percent, the cost of capital for preclinical research in the most frequently quoted estimate from the 1993 OTA report, the cost basis increases by 48 percent in 3 years, doubles in 5.3 years and triples in 8.4 years. In DiMasi's 1991 paper, he presents one set of estimates using a 15 percent discount rate, and 11.8 years to market. In 1998 dollars, the total cost of development was $502 million, of which $347 million were capital costs.

Table 2
Years Cost basis will double
under different opportunity cost of
capital assumptions

Cost of Capital	5%	9%	14%
Years	14.2	8.0	5.3

By shaving years off the estimated time for development of the 14 existing HIV/AIDS drugs, the estimated costs of development fall sharply. When one considers the fact that in many cases the company was not even the source of the pre-clinical research, the bottom follows out of the cost basis.

Another area where there are large differences in costs concerns the size and duration of clinical trials. The 1993 OTA report on the costs of drug development presented this data on the size of

clinical trials. The data were used to indicate the size and upward trend of clinical trials.

Table 3
OTA estimates of Mean Enrollment in Clinical Trials Prior to DNA
1978 to 1983, 1986 to 1990

	1978-83	1986-90
Antihypertension drugs	1,791	2,485
Antimicrobial	1,885	3,461
Nonsterodidal antiflammatory	3,036	3,575

Source: Chapter 3, page 65, 1993 OTA report, Table 3-8: Mean Enrollment in Clinical Trials Prior to New Drug Application, 1978-83, 1986-90. 1993, the Office of Technology Assessment, Pharmaceutical R&D;: Costs, Risks, and Rewards, OTA-H-522, GPO stock #052-003-01315-1, NTIS order #PB93-163376.

We are examining the data from NDA applications HIV/AIDS drugs, to determine the size of the trials. There are the preliminary data from two therapeutic classes of HIV/AIDS drugs.

Table 4
Number of Patents in Clinical trials
discussed in FDA NDA approval
(data complete for two classes of HIV/AIDS drugs)

Protease Inhibitors

Saquinavir	1,265
Ritonavir	1,583
Indinavir	1,262
Nelfinavir	605
Amprenavir	736
Average:	1,109

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

Nevirapine	549
Delavirdine	2,452
Efavirenz	928
Average:	1,310

Note that all of these trials are smaller than the 1986 to 1990 averages of the three drug categories examined by OTA. It was also the case that the US government sponsored some of these trials. For example, for all three of the NNRTI drugs, the US government sponsored or cosponsored trials used in application for an NDA.

Table 10
DiMasi, et al's 1991 Estimates of the Costs of Drug Development

In 1998 dollars

	out of pocket per approval		with Capital Costs @ 5%		with Capital Costs @ 9%		with Capital Costs @ 15%	
Preclinical	89	57.9%	145	63.3%	212	67.5%	365	72.7%
Clinical	65	42.1%	84	36.7%	102	32.5%	137	27.3%
Total	155	100.0%	229	100.0%	313	100.0%	502	100.0%

Table 11
DiMasi et al 1991 estimates: out of pocket and capital costs compared
1998 dollars, capital costs at 9 percent

	out of pocket p/app	Capital Costs @9%	total	out of pocket p/app	Capital Costs @9%	total
Preclinical	89	122	212	28%	39%	67%
Clinical	65	37	102	21%	12%	32%
Total	155	159	313	49%	51%	100%

Table 12
DiMasi et al 1991 estimates: out of pocket and capital costs compared
1998 dollars, 15 percent capital costs

	out of pocket p/app	Capital Costs @15%	total	out of pocket p/app	Capital Costs @15%	total
Preclinical	89	276	365	18%	55%	73%
Clinical	65	72	137	13%	14%	27%
Total	155	347	502	31%	69%	100%

Table 13
US R&D spending by Pharmaceutical Companies and US DHHS
(billions of US dollars)

	PhRMA Survey	IRS* Returns	DHHS** R&D
1991	$ 7.9	$4.4	$ 9.8
1992	$ 9.3	$5.1	$ 9.1
1993	$10.5	$5.9	$10.5
1994	$11.1	$6.6	$10.4

*Form 6765 qualifying expenditures
** NSF's Survey of Federal Funds for Research and Development

Table 14
14 HIV/AIDS drugs
sponsorship of clinical trials, CRISP grants
and time to Market
(Survey November 1999)

	gov/non-gov trials in ACTIS	% gov	CRISP grants	patent app to NDA
Nucleoside Analogue Reverse Transcriptase Inhibitors (RT)				
Zidovudine (AZT)/Retrovir	314/189	62%	1,462	1.5 yrs
Didanosine (ddI)/Videx	131/59	69%	66	4.2
Zalcitabine (ddC)/Hivid	43/26	62%	6	4.9
Stavudine (d4T)/Zerit	53/56	49%	158	7.5
Lamivudine (3TC)/Epivir	65/54	55%	191	6.8
Abacavir/Ziagen	19/29	40%	2	8.0
Protease Inhibitors				
Saquinavir/Invirase	25/32	44%	29	5.0
Ritonavir/Norvir	30/28	52%	43	0.9
Indinavir/Crixivan	53/54	50%	91	2.9
Nelfinavir/Viracept	40/41	49%	25	5.7
Amprenavir/Agenerase	14/11	56%	1	5.4
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)				
Nevirapine/Viramune	42/23	65%	151	2.9
Delavirdine/Rescriptor	20/20	50%	53	3.1
Efavirenz/Sustiva	22/17	56%	1	3.3
AVG:		55%		4.4 yr

Table 15
U.S. Orphan Drug Credit and
Pre-Tax Private Sector Expenditures on Clinical Trials
(thousands of US dollars)

Year	Credit	Approvals	Pre-tax Expenditure	$/drug
1983	236	2	472	236
1984	105	3	210	70
1985	204	6	408	68
1986	6,530	5	13,060	2,612
1987	5,154	9	10,308	1,145
1988	8,053	8	16,106	2,013
1989	14,190	10	28,380	2,838
1990	15,637	12	31,274	2,606

1991	18,475	12	36,950	3,079
1992	17,826	13	35,652	2,742
1993	20,486	13	40,972	3,152
83-93	106,896	93	213,792	2,299

Source: US IRS