OPINION

Call For More Reliable Costs Data On Clinical Trials

By James Love

In February 1993, the now defunct US Office of Technology Assessment issued a report on pharmaceutical R&D, commissioned to provide lawmakers with an independent analysis of the cost of developing a new drug (OTA-H-522). While the OTA report is full of numbers on countless topics, most people are aware of just one. The OTA said $359 million was the "upper bound on the full cost of bringing New Chemical Entities to market." This figure has been used by the multinational pharmaceutical companies to justify the ever-increasing prices for new drugs.

However, many readers of the report were struck by the paucity of independent data collection, and the reliance upon pharmaceutical company consultants for the core findings. Stripped to the core, the 1993 OTA report was simply a restatement of a 1991 paper from the Journal of Health Economics, by four economists with well-known ties to the industry.

In that paper, Joseph DiMasi and Louis Lasagna from Tufts University, Henry Grabowski from Duke and Ronald Hansen from the University of Rochester put the cost of developing a new drug at $231 million, in 1987 dollars. Because of the industry's close ties to the report's authors, and because the Pharmaceutical Manufacturers Association (now the Pharmaceutical Research and Manufacturers of America) published a version of the 1991 study under a PMA cover, the study was widely seen as an industry estimate. This paper, often referred to as the "Tufts" study, was controversial, in part because the figure was far higher than earlier estimates, and also because it relied on data from an unaudited and confidential industry questionnaire.

The OTA did not have access to its own data on R&D outlays, and Congress never issued a subpoena for the data. Faced with this lack of information, the OTA hired Mr DiMasi to recalculate his early estimates using 1990 dollars, and using a range of industry "discount rates" to measure the cost of capital. The $359 million "upper bound" figure was simply the 1991 Tufts study with the numbers adjusted to 1990 dollars, and using a 14% real rate of capital - up from the 9.5% used in the 1991 report. The basis for the Tufts study and the OTA report was a data set which consisted of expenditures on human-use clinical trials and animal testing for 93 NCEs. DiMasi *et al* reported that for the sample, the average out-of-pocket costs of Phase I, II and III clinical trials were $18.9 million, plus $2.8 million for research using animals, or $21.7 million. The $21.7 million was then adjusted for the risk of failure, given an "expected" cost of clinical tests of $48.1 million *per* approved drug.

The authors then made some heroic assumptions about the costs of preclinical research, for which they had no project level data, and assigned $65.5 million in "expected" outlays for preclinical research. Both these numbers were then increased to reflect the opportunity costs of capital, to obtain the $231 million and later $359 million figures so widely used today.

How reasonable are these numbers, given what is known today? There are several areas where skeptics have questioned the PhRMA/Tufts/OTA numbers. First, critics say it is troublesome to apply so much of the industry data, since industry trade associations have incentives to exaggerate costs on all aspects of R&D. Secondly, the assumptions regarding preclinical expenditures are not supported by any project level data. Thirdly, critics say that much of the costs of preclinical and clinical research is paid for by taxpayers.

In an effort to get a handle on this issue, we looked at two sources of public data on drug development costs. The US National Institutes of Health provided my offices with data from 58 clinical trials funded in the 1996 and 1997 financial year budgets. We also obtained from the US Treasury Department 11 years of data from the now-defunct Orphan Drug Tax Credit. Data from these sources suggest direct

industry outlays on R&D for many drugs may be far less than has been imagined.

Orphan Drug Tax Credit

From 1983 until 1994, the US government offered a tax credit to support the development of orphan drugs. The tax credit was for 50% of the direct expenditures on human-use clinical trials. From 1983 to 1993, some 93 orphan drugs were approved for marketing. During that same period, companies received $106.9 million in tax credits. In order to obtain these credits, companies reported direct expenditure on clinical trials of $213.8 million, or $2.3 million *per* approved drug.

One expects some lag time between the beginning of the tax credit and the drug approvals, so we looked at the results beginning in 1989, the seventh year of the tax credit program, until 1993. During this five-year period, 60 orphan drugs were approved, while tax credits of $86.6 million were taken, or about $2.9 million *per* approved drug. This amount was fairly consistent from year to year. In 1995 dollars, the amount expended on human-use clinical trials was $3.2 million *per* approved drug, from 1989 to 1993.

What are we to make of this data (table below)? DiMasi *et al* say that the average out-of-pocket cost of human-use clinical trials is $18.9 million in 1987 dollars, or $24.5 million in 1995 dollars. With these numbers adjusted for failures, they calculate the average "expected cost" of human use clinical trials (*per* approved drug) at $42.3 million in 1987 dollars, or $54.8 million in 1995 dollars. In the study, the average was significantly higher than the median, and for the median the expected cost of human-use clinical trials would be $23.7 million and $30.7 million. But no matter how you slice it, it is hard to reconcile the DiMasi data with the data from the Orphan Drug Tax Credit. The differences are very large.

There are three possible explanations. First, it is possible that not all companies conducting human-use clinical trials claimed the Orphan Drug Tax Credit on tax returns, for example if the company was not profitable. However, this cannot explain the entire disparity. In 1987, the OTA said some six firms with assets greater than $250 million claimed $4.7 million in orphan drug tax credits. This implied expenditures of $9.4 million, or $1.6 million *per* firm. In 1987, nine orphan drugs were approved for marketing, and over the next five years an average of 12 drugs were approved for marketing every year. The amount of reported expenditures, even from these six firms, seems low.

Another explanation is that the government, rather than the companies, actually paid for the orphan drug human-use clinical trials. Indeed, it would seem that this must be the case, since the reported expenditures under the Orphan Drug Tax Credit are less than 8% of the expenditures predicted by the PhRMA/Tufts/OTA data. Taken by itself, this would suggest that 92% of the costs of human-use clinical trials for orphan drugs is paid for by the taxpayers, rather than the drug firms.

The third scenario is that the PhRMA/Tufts/OTA numbers are too high. Based on clinical trial data from the NIH, we calculated the expected costs, using the same "hazard rates" for success that were used in the DiMasi study. Thus, for example, a dollar spent on Phase I trials is multiplied by a factor of 4.35 to reflect the risks of failure. The average and median out-of-pocket costs for combined Phase I, II and III trials were $7 million and $4.6 million for the NIH-funded trials, and using 1995 dollars, the PhRMA/Tufts/OTA figures were $24.5 and $14.3 million, three times as high.

US Orphan Drug Credit ('000 dollars)

Year	Credit	Approvals	Expenditure	$/drug nominal	Expenditure 1995 dollars	$/drug 1995 dollars
1983	236	2	472	236	695	348
1984	105	3	210	70	297	99
1985	204	6	408	68	559	93
1986	6,530	5	13,060	2,612	17,447	3,489
1987	5,154	9	10,308	1,145	13,352	1,484
1988	8,053	8	16,106	2,013	20,117	2,515
1989	14,190	10	28,380	2,838	34,016	3,402
1990	15,637	12	31,274	2,606	35,953	2,996
1991	18,475	12	36,950	3,079	40,841	3,403
1992	17,826	13	35,652	2,742	38,353	2,950
1993	20,486	13	40,972	3,152	42,959	3,305
83-93	106,896	93	213,792	2,299		2,630
89-93	86,614	60	173,228	2,887		3,202

Cost Of NIH And Industry Clinical Trials ('000 dollars)*

No of observations	NIH	P/T/O (95 $)
Ph I	6	87
Ph II	12	70
Ph III	40	36
Average cost of trials	6,986	24,467
Average expected cost	16,106	54,816
Median cost	4,604	14,268
Median expected cost	11,490	30,675

* corrected from original publication

One partial explanation for the differences between the PhRMA/Tufts/OTA data and the NIH budget numbers could be treatment of overheads. The NIH numbers appear to reflect direct expenditures on clinical trials, while the PhRMA/Tufts/OTA may include generous overhead allowances. In a small number of cases, the NIH trials involve cooperative R&D agreements, which may involve some industry cost sharing, such as with Taxol (paclitaxel), where Bristol-Myers Squibb provided the NIH with 17 kilos of Taxol for use in NIH-sponsored trials. This is an area for further research. It is also possible that the PhRMA/Tufts/OTA data was biased, given the incentives to the industry to overestimate private-sector R&D costs.

Our initial view is that the huge disparities between the Orphan Drug Tax Credit data and PhRMA/Tufts/OTA estimates of drug development costs are explained by a combination of all three factors - some unclaimed tax credits, a large role by the government in the development of orphan drugs, and overstating of costs by the industry in the PhRMA/Tufts/OTA study. The differences also point to the need for disclosure to the public of more reliable data from the industry, so policy makers can better evaluate industry R&D costs. *James Love is director of economic studies at the Center for Study of Responsive Law in Washington, USA.*