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Discussion

Extraordinary claims require extraordinary evidence

Donald W. Light^{a,b,*}, Rebecca N. Warburton^c

^a *University of Medicine and Dentistry of New Jersey, Stratford, NJ 08084, USA*

^b *Center for Bioethics, University of Pennsylvania, USA*

^c *Michael Smith Foundation for Health Research Scholar, School of Public Administration,
University of Victoria, Vic., BC, Canada*

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1. Extraordinary claims require extraordinary evidence

At the beginning of 2003, the *Journal of Health Economics* published a paper of great importance in public policy by DiMasi, Hansen, and Grabowski (referred to hereafter as “DHG 2003”). The paper is based primarily on confidential, proprietary data supplied by pharmaceutical companies to the Tufts Center for the Study of Drug Development, a research center that receives significant unrestricted grants from pharmaceutical companies (TCSD, 2004a,b). This commentary is intended to invite discussion among health economists and other researchers about the quality of data and sampling used in estimating the costs of pharmaceutical R&D.

DHG 2003 estimates that it costs \$802 million on average (in 2000 dollars) to research and develop a self-originated new chemical entity, including failures and cost of capital. It is worth noting that after adjusting for inflation, the DHG 2003 cost estimates are roughly two to four times as high as other estimates of pre-approval drug R&D costs (Love, 2003; Public Citizen, 2001; OTA, 1993). The 2003 article represents a sophisticated analysis that builds on the authors’ equally important article in 1991, and adds several refinements and extensions of that prior analysis. There are, however, problems with the data and sampling on which these results depend, and this commentary focuses on those problems.

* Corresponding author. Tel.: +1 609 915 1588; fax: +1 609 924 1830.
E-mail address: dlight@princeton.edu (D.W. Light).

A careful review of the article identified six serious sources of doubt about the validity and usefulness of the source data and methods used in DHG 2003:

- (1) First, the inherent comparability and reliability of the survey data must be questioned because of variations in internal company cost allocation methods over time and across companies. Because cost data used was proprietary and confidential, readers cannot know how each company collected its data, or what was counted as research costs, and no independent verification of the accuracy of the information is possible. Firms reported R&D expenditures stretching back more than 10 years (to 1980), during which several firms underwent mergers and/or changed accounting systems or practices. The degree of potential variation is large, and these many variations in practice may compound on each other, making any point estimate misleading. (Internal validity)
- (2) Second, considering the clear interest of pharmaceutical companies in higher (rather than lower) estimates of drug development costs, and sampled firms' likely awareness of the intended use of the survey data, it is not unlikely that companies would deliberately and systematically overstate costs in their survey responses (OTA, 1993). The survey design did not permit independent review of the reported costs, so upward bias cannot be ruled out. (Internal validity.)
- (3) Third, the small, non-random firm sample ($n = 10$) and drug sample ($n = 68$) introduce another potentially large source of variation and error into cost estimates. Although the sampling of drugs was reported to be random, this is misleading, because the selection of firms participating in the survey (which preceded the selection of drugs) was not random (DHG 2003, pp. 157–158); randomization cannot be recovered once lost at the first stage of sample selection. A total of 24 firms were invited to respond; 12 firms accepted and were asked to provide data on an unstated number of drugs, randomly selected from those companies' drugs in the proprietary database; 10 firms provided usable data, covering development of 76 drugs; but drug data were usable for only 68, and complete for even fewer (it is noted as an example that only 66 drugs had Phase I trial cost data). No information is provided about how invited firms were selected, nor whether they were selected from the universe of all US research-oriented pharmaceutical firms or some other less representative universe. The 42% of invited firms that responded (10 of 24) self-selected, and given the industry interest in higher cost estimates it cannot be ruled out that firms with higher than average costs were most likely to choose to participate. (Internal validity)
- (4) Fourth, the findings concern U.S. "self-originated new chemical entities" (NCEs; drugs that were researched, discovered, and developed in-house), whose costs are higher than those for more typical "new" drugs. Only 35% of new drugs approved by the FDA (from 1990 to 2000, FDA, 2004; from 1989 to 2000, NIHCREG, 2002) contained a new molecular entity, and only 62.4% of the survey firms' approved NCEs were said to be self-originated (DiMasi et al., 2003b, p. 3, note 1). Thus "self-originated new chemical entities" represented about 22% (62.4 of 35%) of new drug approvals. The number of truly self-originated NCEs may be even smaller, because the authors note that all phases of work may not have been done in-house and because there are well-documented examples of companies making such claims that do not comport with the facts (Mitsuya et al., 1989 Weinhold General Accounting Office, 2003). This might

not matter much, in terms of estimating typical drug development costs, if all drug development costs were similar, but they are not. According to DiMasi et al., 1991 (footnote 48), self-originated NCEs are 3.7 times more costly to develop than acquired or licensed-in NCEs, and many times more costly than new formulations, combinations or administrations of existing drugs. The DHG 2003 estimates therefore pertain to the most costly 22% of new drugs. (External validity.)

- (5) Fifth, estimates of company spending on drug development are presented without deducting (or at least identifying) government subsidies to this work. The industry receives taxpayer funds from the NIH and other agencies, though amounts are not disclosed at the request of drug companies (General Accounting Office, 2003; National Science Foundation, 2003). Given the use of cost data to justify drug prices and patent protection, private (company-paid) cost and not social (total) cost is the policy-relevant figure. (External validity)
- (6) Finally, the cost estimates are not adjusted for tax deductions and credits. Drug R&D expenses are fully tax-deductible each year, and there are special drug R&D tax provisions. The OTA (1993) estimated that tax savings and tax credits reduced R&D spending by nearly 50%. Lower tax rates in the 1990s might reduce that figure somewhat, but pre-tax costs clearly overstate true private (company) costs by a substantial percentage. (External validity)

These significant concerns about internal and external validity call the study results into question. Good science depends on different investigators analyzing the same data. Yet this science-based industry refuses to allow independent parties to check the validity of their cost data and analyze it so that policy can be based on solid, objective, reproducible evidence.

The estimate of R&D cost in this article is widely cited and accepted as an authoritative “fact” in the press and in the highest national and global policy circles. Given the prominent use of these cost estimates by the pharmaceutical industry and its advocates to influence national and international policies, it is critical that they be scientifically valid and relevant to the policy uses made of them. Shortly after DHG 2003 appeared, the Tufts Center for the Study of Drug Development announced that the average cost of developing a self-originated new chemical entity, including post-approval studies, was \$897 million (TCSDD, 2003; Kaitin, 2003; DHG 2003). This figure, like the ones that preceded it, is based on confidential, unsystematic data, and has dubious scientific validity. In addition, adding post-approval studies to the costs of R&D is inherently questionable, because these “seeding trials” are designed primarily to familiarize physicians with the new drug and encourage its use; they are rarely randomized or blinded, but instead feature open-label case series, and are often sponsored by company marketing departments (Kessler et al., 2004).

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