Were the Harvard editors fair?

Decide for yourself

We recently published an article in the Harvard Health Policy Review (Vol 9 (1):58-68 http://www.hhpr.org/currentissue/) concerning our experience publishing a critique of an article in the Journal of Health Economics. In response the three JHE editors, who are professors of health economics at Harvard, have said they followed standard editing procedures and only deleted "personal attacks" against the authors of the famous article we were critiquing. Are they right? Decide for yourself.

It is important to know that the article we were critiquing was the latest in a widely promulgated series, much cited by the pharmaceutical industry to persuade policy makers and payers that R&D costs are huge and thus prices need to be very high and patent protection periods long. We refer to this paper as DHG 2003.

Below we detail the series of three deletions from our critique. This material was never printed in the Journal.. Editors of academic journals almost never go in and delete authors' materials.

First Deletion, two paragraphs concerning connections between funding and research results:

> Underlying—or perhaps overshadowing—these methodological shortcomings is the issue of competing interests. Given the strong known connection between industry funding and research results favorable to the industry, disclosure of industry connections in published work is essential. Two recent reviews found that industry-sponsored research is 3 to 4 times more likely to report results favorable to the sponsors than articles with independent funding (Bekelman, Li, and Gross 2003; Lexchin, Bero, Djulbegovic, and Clark 2003). Considering the clear interest of pharmaceutical companies in higher (rather than lower) estimates of drug development costs, it is worth noting that the DHG 2003 cost estimates are much higher than other estimates of R&D costs (Love 2003, OTA 1993).
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> Medical journals using the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* adhere to strong and clear criteria concerning real and potential conflicts of interest (ICMJE 2003). The minimum requirement is full disclosure by authors to editors and reviewers, and by journals to readers. DHG 2003 did not disclose any industry funding or competing interests, and simply stated "The authors did not receive any external funding to conduct this study." Yet the web site (2004) of the Tufts Center for the

> Study of Drug Development (where DiMasi is Director of Economic Analysis) explains clearly that pharmaceutical and biopharmaceutical companies are major funders of the organization (TCSDD 2004a, 2004b). While the bulk of the Center's support (65%) is apparently in the form of unrestricted grants, the potential for conflict of interest remains. Suppose that research results damaging to the pharmaceutical industry were routinely published by the Center. In that case, what would happen to the level of industry funding over time? Would the industry continue to supply the confidential, proprietary information which is the basis of much of the Center's research?

You be the judge: Does this material strike you as "personal attack"? We did not think so and objected. The Harvard editors stood firm: they would allow no material that discussed the known correlation between funding source and study results, or that disclosed the drug industry funding received by the authors. The editors claimed we were discussing their motives; our view was that we were merely pointing out that readers had not been informed of an important fact with the potential to influence the study's results.

What do you think?

Recently, the New York Times put on its front page (Oct 22, 2008) an article discussing how financial conflict of interest and ideology bias economists' estimates of how much universal health care will cost. Those paid by McCain claimed that will cost $6 trillion over 10 years for Obama to offer subsidized health insurance to people with low incomes, while economists paid by Obama estimated it would cost $1.17 trillion. Is this a personal attack on those economists?

Second Deletions

After exhibiting bias by allowing the authors far more time to write a reply and not keeping their reply tightly limited to the issues raised (as they did us), the editors insisted on deleting a second set of passages about funding and study bias, in ***bold italics*** below. They also considered stating the principal author's job title as a personal attack!

> In the case of this study, the authors said they received no external funding, ***but this very complex, long study of at least two years' duration was funded from somewhere. From a budget internal to the Center? International disclosure rules for possible bias due to commercial funding call for wider disclosure.*** The web site (2004) of the Tufts Center for the Study of Drug Development ***(where DiMasi is Director of Economic Analysis)*** explains clearly that pharmaceutical and biopharmaceutical companies are major funders of the organization.
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> [Several examples of non-research costs being included in corporate R&D] ***"raise serious questions about any estimate based on self-reported, confidential data from companies who***

have benefited greatly for 50 years from inflating cost estimates. The simple question is this: If the industry really has such large R&D costs and wants society to help it pay for them, why does it not open its books to data validation?"

Regarding the truthfulness of data reported by the drug companies, the authors erroneously claim that since everyone knows that "drug development is in some sense costly, risky and lengthy," there is "little reason for firms to fabricate…" On the contrary, there is every reason to exaggerate cost, risk and length, as the drug companies and their 625 registered lobbyists tirelessly do and have since the 1950s.

Their Reply details all the ways in which most new drugs are very different from the self-originated NMEs that they sampled. They further advanced this error in their press conference announcing their main conclusions more than a year before the article appeared, and by making no known objection as the pharmaceutical industry has repeated over and over that the cost of R&D for "the average new drug" is $802 million. To our knowledge, the authors have never objected to this gross misattribution of their findings to all "new drugs," when serious researchers everywhere immediately object to their research being misrepresented.

Again, you be the judge. Were the Harvard editors protecting the authors from personal attack? Why were they deleting relevant material to our questioning the high estimates of how much research costs the pharmaceutical industry.?

We protested these deletions and received what we later termed ultimatum editing: "accept our chops" (as they put it) or don't get published.

Third Deletions

After finally accepting and sending our critique, the authors' reply, and our rejoinder to Elsevier for copy-editing and then page proofs, the editors suddenly pulled the entire set out of production with no explanation. Neither of us had ever encountered this before in academic publishing, or ever heard of it happening to anyone else. Weeks later, the editors suddenly sent us their "revisions" of our already short Rejoinder piece, with 100 of 132 lines deleted! See the attached file. You be the judge of whether what was deleted contained personal attacks on the authors.

Professor McGuire recently told the reporter from *The Scientist* that "Light and Warburton's accusations are 'far-fetched' and 'bullshit'"… Our article recounting these actions is now called a "personal attack" on the editors! We did not intend that and believe our HHPR piece gives a factual account of the editors' (and our) actions. We take responsibility for our actions and hope the Harvard editors will do the same.

Calling our account a "personal attack" is a classic tactic used by perpetrators and described in William Ryan's classic, "Blaming the Victim".

You be the judge, and please read our article in the HHPR piece for a fuller account of our experience.

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~~Reply~~ Rejoinder

Setting the record straight in the Reply by DiMasi, Hansen and Grabowski

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In our commentary on the very long and complicated article by DiMasi et al. (2003), we limited ourselves to six briefly stated points about the authors' actual research. We therefore did not address the wide range of other studies that they invoked in order to validate their data set, but instead focused on specific problems of internal and external validity that mean no estimate based on them should be given any credence. It is wrong for the authors to imply at the beginning of their Reply that we did not read carefully "the numerous validations of our results obtained from alternative data sources and analyses that were reported…." We have read every word of this 31-page article several times.

not only more rigorous for accuracy

The authors' section on Validation is devoted to using other confidential industry sources to show that their sample reflected national patterns, that the rate of *increase* in trial sizes and costs and R&D personnel helped explain why their estimates are significantly higher than their previous study, and that their estimate of out of pocket costs was within a range estimate they made by using data from the Pharmaceutical Research and Manufacturers of America. These validation efforts do not address the central question raised by the OTA study (1993, pp. 41, 54–60), of the underlying cost figures themselves submitted by the companies being ~~inflationary~~ and unverifiable. Concerns about industry sources have since been evaluated more systematically in two reviews that found that articles in major refereed journals based on industry-sponsored research are three to four times more likely to report results favorable to the sponsors than articles with independent funding (Bekelman et al.,

inflated

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2003; Lexchin et al., 2003). We therefore remain unimpressed by these attempts and think our critique of the sample and data stand. In the case of this study, the authors said they received no external funding, but the web site (2004) of the Tufts Center for the Study of Drug Development explains clearly that pharmaceutical and biopharmaceutical companies are major funders of the organization.

The authors also erroneously mischaracterize these studies of drug development as serving "the business, not political, concerns of pharmaceutical firms." For nearly 50 years, the pharmaceutical industry has made the costs of research and development the center of their political concerns, in order to enhance their business (Goozner, 2004; Scherer, 2004, 13 September). The industry depends heavily on government regulations and various forms of tax subsidies. It has worked ceaselessly to increase that dependency and its profitability by extending tax subsidies and governmental protections from normal competition (Temin, 1980; Hunt, 2000; Hilts, 2003).

The authors in their Reply (concerning the validity of their research) rely heavily on the OTA study. They cite it five times and erroneously write that "... the OTA study concluded that the data used for our previous study were valid." Rather, the most favorable statement in the OTA report is on p. 65: "Although the cost estimates of bringing an NCE to market are imprecise and potentially biased, corroborative evidence from the aggregate studies suggests they are not grossly overestimated." This statement cannot reasonably be construed to mean that the data are valid; only that despite being imprecise (which supports the point in our commentary about variability), they cannot be shown to be hugely overstated.

In its review of data validity, the OTA noted that stock purchases, mergers and acquisitions with research-based firms might be included in R&D figures, as might generous handling of indirect and overhead costs, such as revamping a company's entire computer system. The report observed, "how companies allocated these expenses to specific NCEs (new chemical entities) for the purpose of the survey is unknown" (p. 57). And later (p. 58), "the accuracy of these estimates depends on the capacity of the firms ... and on their motivation to report such expenditures accurately ... a company that understood the use to which the data would be put and with a strategic incentive to overestimate the preclinical ratio could do so without potential for discovery." Given that all the data are submitted to the Center at Tufts under strict rules of confidentiality, the potential for discovery is zero. In an interview about the present 2003 study with F.M. Scherer after its results had been announced, he said that pharmaceutical corporations include as part of R&D expenditures, the legal and lobbying costs of protecting patents, the extensive interviewing of physicians to gather information about a product and its market, the costs of oversized clinical trial much larger than required by the FDA, and the large payments to physicians, clinics and hospitals for finding and monitoring patients for trials as "bribery" (Scherer, 2002, 4 December).

Regarding the authors' failure to deduct taxpayer subsidies from the R&D costs to pharmaceutical firms, they claim that taxes are on *profits* and that our claim that taxes intimately involve deductions and credits is "erroneous." Any course on tax law recognizes that tax code concerns deductions and methods for arriving at the figure, "taxable profits." Companies are well aware that spending more on R&D reduces their taxable profits and leads directly to lower taxes; they would be irrational if this did not influence their R&D spending. After-tax costs are therefore the correct ones to use.

Finally, also in the section on tax subsidies, the authors state that tax credits amount to only 2% of R&D expenditures. This is erroneous in three ways. First, the Congressional Research Service's review of federal taxation for the drug industry concludes, "... from 1990 to 1999, its average tax liability after credits (except foreign tax credit) was 71% of its average tax liability before credits." This equaled US$ 3.2 billion in 1999 and included the orphan tax credit but not the research and experimentation tax credit, valued at US$ 0.7 billion in 1999, for a total of US$ 3.9 billion. But a proper treatment of taxes, according to the Director of Research for the Internal Revenue Service (Mazur, 2002), would include the possession tax credit, worth US$ 10 billion in 1990 (Guenther, 2002) and about US$ 20 billion or its equivalent in Ireland in 1999. Together, these equal US$ 23.9 billion in tax credits when the industry trade association reported R&D investments of US$ 18.5 billion. In short, a good analysis of tax deductions and credits for the pharmaceutical industry has not been done, but one can make a plausible case that taxpayers pay for all the industry's research and development costs. Certainly the amount is far higher than 2% of R&D expenses.

The authors' next turn to our central point about several sources of variability that can multiply on one another so that one cannot know what actual costs might be if measured and cleaned according to accepted research practices. They claim that we said wide variability in costs would bias a point estimate, when in fact we did not mention bias at all; we simply pointed out that point estimates inherently lose their validity and usefulness as variability increases. If variability is wide, a point estimate is pointless and misleading, in that it conceals the variability. Reporting that "R&D Costs of Major New Drugs Range from US$ 300 million to US$ 1300 million," is very different from reporting that costs average US$ 800 million, even if both reports are technically correct. Our point was that in order to provide a useful estimate, the authors should have provided a range estimate rather than a point estimate.

The authors next turn to our critique that their sample size is small, non-random and drawn from an unstated universe. They pass over the small, non-random sample of ten firms to emphasize "hundreds of observations across many firms." This refers to each of the data points for the 68 or fewer drugs from the 10 self-selected firms out of the 24 invited firms and gives the erroneous impression that their sample was very large. The key variables were firms and drugs, not observations per drug.

The authors erroneously misstate that we claimed government funds were included in "self-originated" R&D. They point out that their cost data "reflect only private resources" and "excluded government grants...." We flagged the need to deduct government funds because the authors wrote in footnote 8: "this does not preclude situations in which the firm sponsors trials that are conducted by or in collaboration with a government agency, an individual or group in academia, a non-profit institute, or another firm," which appears to indicate that some trials paid for at least with partly with government funding might be included. There is no statement about such amounts being subtracted, deducted, or excluded in the DHG 2003 paper. Here, in their Reply they provide new information about this issue and should say so rather than indicating that we erred in interpreting their paper.

The authors also misrepresent us when they say that we "maintain" the R&D costs of licensed-in NMEs are much lower than self-originated NMEs. We merely cited their stating that the latter cost on average 3.7 more than the former. The authors then claim that we "grossly misconstrued the meaning of the ratio," because other firms (or governments or

foundations) had to pay for all the earlier R&D costs. That claim misrepresents their own ratio and is beside the point, which is how much less licensed-in NCEs cost the ten firms in their sample. The authors also claim that we "question the classification of drugs into self-originated and licensed," when we did not.

The authors also claim another error but then affirm its veracity when they say that we confound the R&D costs of NMEs with non-NMEs and do not realize that only a small fraction of "new drugs" are NMEs. Any analysis that confuses this distinction "is methodologically flawed," they write. We agree and thank them for detailing why their estimate of R&D costs is not related to the vast majority of FDA-approved "new drugs," most of which (as they state) have substantially lower R&D costs and a higher success rate of being approved. But while the authors write that they "clearly described what we sampled," they misrepresented their main conclusion in their own Abstract by stating, "The estimated average out-of-pocket cost per new drug is . . ." Their Reply details all the ways in which most new drugs are very different from the self-originated NMEs that they sampled.

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