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Reply

Setting the record straight on setting the record straight: Response to the Light and Warburton rejoinder

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In Light and Warburton's (2005b) rejoinder (hereafter, Rejoinder) to our reply (DiMasi et al., 2005; hereafter, Reply), the authors reiterate some erroneous assertions made in their original comment (Light and Warburton, 2005a; hereafter, Comment) and add unsubstantiated insinuations of bias on the part of the now defunct US Congressional Office of Technology Assessment (OTA) and of academics and others who served on the OTA's Advisory Panel for its report on pharmaceutical R&D (OTA, 1993). We will address Light and Warburton's points briefly here as they appear in the Rejoinder.

Light and Warburton claim that the validation exercises in our R&D cost study (DiMasi et al., 2003; hereafter, DHG) did not address concerns about whether the data that we obtained were inflated by the survey respondents. Assessing whether our results were substantially too high or too low was the whole point of the validation efforts.[1] We expanded our efforts in the recent study beyond those that the OTA used when assessing our previous study (DiMasi et al., 1991; hereafter, DHGL). We utilized results obtained by independent investigators,

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[1] More recently, two US Federal Trade Commission (FTC) economists have drafted a paper that analyzed pharmaceutical R&D costs using estimates of development times and success rates obtained from information in a publicly available commercial database of investigational drugs (Adams and Brantner, 2004). They found, for roughly the same period as for our study, a somewhat higher estimate of capitalized cost per approved new molecular entity (NME) (US$ 868 million dollars in year 2000).

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government statistics, audited financial statements, industry-wide survey data collected and reported on an annual basis over decades, and information gathered by database vendors over many years. We combined and utilized some of these data in ways that, to our knowledge, had never been done before.

To suggest that the validation efforts that the OTA and we made should be dismissed is to give little or no weight to the fact that our sample data are consistent in a significant number of ways with a wide variety of publicly available data sources. Maintaining that position requires that one believe that the entire industry, financial auditors, government data collection processes, and vendors whose sales are dependent on providing business intelligence that their customers perceive to be reliable engaged in or were misinformed by a highly coordinated and detailed collusive effort held together over decades prior to when our study was conducted. We reject unsubstantiated conspiracy theories. Like the OTA, we accept the validation efforts as reasonable checks on our results.[2]

In the Rejoinder, Light and Warburton cite some speculative statements from the OTA report, but the OTA's overarching summary quote, which we noted both in DHG and in the Reply, shows that the OTA ultimately concluded that the estimates in DHGL were "reasonably accurate".[3] The quote in the Rejoinder from the OTA report regarding "aggregate studies" suggesting that the estimates in Hansen (1979) and DHGL were not grossly overestimated refers to only part of the corroborative evidence that the OTA examined. What's more, the aggregate studies to which they referred yielded estimates that were uniformly somewhat *higher* than the corresponding estimates in Hansen (1979) and DHGL.

Unfortunately, the Rejoinder either explicitly or implicitly casts aspersions on the integrity of distinguished members of the OTA Advisory Panel, OTA's process for developing its reports, the OTA's oversight Technology Assessment Board (TAB)[4] and the OTA researchers themselves. The Chairman of the OTA Advisory Panel for its report on pharmaceutical R&D, F.M. Scherer, is an eminent industrial organization economist who was a former chief economist for the FTC, and who has served on many government panels. His reputation is beyond reproach and he needs no defense. Light and Warburton are unclear about which two of the other economists on the Panel are suspect in their minds or what research of theirs they find objectionable. The presence of industry representatives on the

[2] Light and Warburton's dismissal of all of our validation efforts in the Rejoinder is particularly curious given their implicit endorsement in their Comment of the Public Citizen (2001) analysis of R&D costs. As we explained in our Reply and in more detail in DiMasi et al. (2004), the Public Citizen analysis was deeply methodologically flawed. However, it was also the same type of validation exercise as one that we used in both DHGL and DHG, and it used the same basic data. It is logically inconsistent to accept the Public Citizen analysis as a reasonable measure of R&D costs, yet reject our validation effort because of the nature of the data used. If one accepts the general methodological approach as valid, then the only issue is who correctly analyzed the same data.

[3] "To summarize, the estimates by DiMasi and colleagues of the cash outlays required to bring a new drug to market and the time profile of those costs provide a reasonably accurate picture of the mean R&D cash outlays for NCEs first tested in humans between 1970 and 1982" (OTA [1993, p. 66]).

[4] The TAB consisted of six Senators and six Representatives with equal representation from each party, and the Director of the OTA. The TAB was assisted by an advisory council of "10 eminent citizens from industry, academia, and elsewhere outside the federal government" (http://www.wws.princeton.edu/~ota/ns20/proces_f.html; accessed June 12, 2005). The TAB reviewed for approval all major studies.

Panel is not surprising, nor is there anything wrong with that.[5] Even critics of the pharmaceutical industry have lauded the work of the OTA.[6] The Rejoinder references eight members of the Panel, but the Panel consisted of 16 members, including consumer advocates.

The Rejoinder notes that DiMasi was listed in the OTA report as a Principal Contractor,[7] and it suggests that DiMasi was involved in the OTA's evaluation and estimation of R&D costs. This is false. It would have been inappropriate for DiMasi to work on the OTA's evaluation or estimation of R&D costs, and he did not work on that part of the report. The OTA report was wide-ranging and it extended well beyond its one chapter on evaluating R&D costs. At the OTA's request, DiMasi provided the OTA with Tufts Center for the Study of Drug Development (CSDD) data on new drug regulatory milestone dates for given periods.[8] These data were analyzed by the OTA, along with similar data obtained directly from the Food and Drug Administration (FDA), to examine trends in approval rates and approval times in a chapter describing government regulation of pharmaceutical R&D (OTA [1993, p. 161]). The data were not used in the chapter that evaluated existing R&D cost estimates.

We discussed tax issues extensively in DHL, and again in our Reply. As we noted therein, the corporate income tax is intended to be a tax on profits (revenues minus costs), not sales. In the Rejoinder, Light and Warburton persist in erroneously viewing deductions of expenses when determining corporate income tax liability as a form of corporate welfare. They state, for example, that spending more on R&D reduces taxes. Nowhere, however, do they recognize the implied future tax liability resulting from sales of the fruits of those R&D efforts or that increasing current R&D spending reduces current after-tax profits. Firms may increase R&D spending because scientific and/or marketplace opportunities improve or because of a true subsidy, such as an R&D tax credit (the magnitude of which we analyzed in DHG), but not because they deduct expenses for corporate income tax purposes.[9]

With regard to direct government funding of R&D, the Rejoinder suggests that Light and Warburton were led astray by a footnote in DHG. When we discussed firms sponsoring trials conducted by or in collaboration with other groups, we thought that it was clear that

[5] According to an assessment of the OTA's process for producing reports, the "OTA worked to ensure that the views of the public were fairly reflected in its assessment. The Agency assembled an advisory panel of stakeholders and experts for each major study to ensure that reports were objective, fair, and authoritative" (http://www.wws.princeton.edu/~ota/ns20/proces_f.html; accessed June 12, 2005). Furthermore, "No attempt was made to develop consensus among panel members; in fact, a wide diversity of views was sought. OTA retained full responsibility for the content and conclusions of each report" (http://www.wws.princeton.edu/~ota/ns20/proces_f.html; accessed June 12, 2005).

[6] For example, Hilts (2003, p. 213) characterized the OTA as "a carefully bipartisan and respected study office".

[7] There were 16 Principal Contractors listed in the report.

[8] The OTA paid a nominal data processing fee to the Tufts CSDD (not to DiMasi) for this information.

[9] As noted in DHG and in our Reply, there are complicated second-order effects from treating what are really investment expenses as if their true economic depreciation rate was 100% for the year in which they were incurred. Light and Warburton's position on tax deductions, however, is made at a first-order level. The flaw in their reasoning can be seen clearly in the context of an extreme example. By their logic, firms would be better off if they are able to deduct more of their R&D expenses. However, firms are able to deduct proportionately more of their R&D expenses only if the corporate income tax rate is higher. To go to the extreme, under Light and Warburton's logic a 100% corporate income tax rate provides maximal benefit to a firm because, in their view, taxpayers would then be covering all of its R&D expenses. However, a 100% tax rate would mean that government is appropriating all of the firm's profits. The firm would then have no incentive to remain in business.

sponsorship implied financial responsibility. Nonetheless, we are pleased that Light and Warburton now better understand our results.

The Rejoinder notes the relevance of examining variability in costs, and claims that a range estimate would have been more informative than a point estimate. It is unclear why a range estimate would be more informative, but a range estimate, nonetheless, is neither possible nor does it make sense here because of fixed costs and the need to account for failures.[10] In any event, Light and Warburton's comments in the Rejoinder on this point appear to suggest that we ignored variability. This is demonstrably false. In DHG, we provied standard deviations for clinical phase costs, sensitivity analyses for key parameters, and the results of Monte Carlo simulations that accounted for simultaneous variability in all of the parameters used to determine the capitalized R&D cost estimate.

As already noted in our Reply, we dispute Light and Warburton's claim that 68 drugs and ten firms is a small sample for the purpose of estimating phase cost means. Furthermore, their comments in the Rejoinder appear to suggest that the statement in our Reply that many of the parameters used to determine our full cost estimate were estimated based on hundreds of observations was really about us just adding up multiple data points for the same 68 drugs. Their implication is false. Our estimates of development times, approval times, the clinical success rate, and clinical phase attrition rates were based on data from larger datasets. Each observation used to estimate every one of those parameters represents a different *drug*. Thus, hundreds of different *drugs* (across many firms) were used to estimate each of these parameter values.

Light and Warburton's first comment in the Rejoinder about seeding trials is just a restatement of suppositions about the veracity of survey respondents. As noted in the Reply and above, our validation efforts address this issue. Their second comment is in part unnecessary and in part irrelevant. They in effect note that if R&D costs are considered on a lifecycle basis for a drug (active ingredient) as we did in DHG, then R&D costs should be compared to the aggregate of profits[11] from all variants of the drug. We agree, but we had already made this point in our Reply, and, as we noted therein, this approach has already been taken in rate of return studies.

As part of their second comment on seeding trials, Light and Warburton also note that in our Reply we reported that many non-NME new drug application (NDA) approvals are for drugs that were first approved more than 25 years earlier. What they do not mention is our point that a substantial number of all non-NME NDA approvals for the period analyzed were for drugs that had likely already long lost patent protection and were obtained by firms that had no relation to the original manufacturer with respect to the drug in question. Light and Warburton appear to be trying to make a point here about so-called "evergreening" of patents. Whatever one wants to say about evergreening, it was not a topic in DHG and it has nothing to do with whether our R&D cost estimates are reliable.

In their Rejoinder, Light and Warburton claim in their Comment that they used a ratio (3.7) relating to expenditures on self-originated and licensed-in drugs in the same way that

[10] Finding a standard confidence interval for the total capitalized cost estimate is also an intractable problem because of the complexities and inherent nonlinearities involved in the method by which a full cost estimate is determined.

[11] Strictly speaking, R&D costs should be compared to net returns, not to profits.

we used it in DHGL. They remain confused about this ratio. The only use we made of that ratio was for one intermediate step in a methodology that utilized published aggregate industry data to validate our results. If one were to do an analysis of the R&D costs of licensed-in drugs it would be necessary to account for the costs incurred by all of the firms that played a role in developing them. And, as noted in our Reply, these drugs do not come to the licensees free. The licensees "pay" for them through the financial parameters of their licensing agreements. It seems clear from Light and Warburton's Comment that their intent was to suggest that there is a class of drugs that we did not consider that are considerably less costly to industry than are the self-originated drugs that we examined. We cannot think of any other reason why they would mention the ratio. The ratio does nothing to support such a contention, and, taken in isolation, it is of no significance.

Finally, we were clear in our R&D cost studies that for pre-approval costs we were considering new chemical and biopharmaceutical entities. Costs for product line extensions are covered by our post-approval cost estimate. As we explained in our Reply and in DiMasi et al. (2004), it is inappropriate to view individual product line extensions as methodologically equivalent to new chemical and biopharmaceutical entities, and therefore, to treat them all as distinct manifestations of the same unit of observation. If product variants are approved after a drug is first approved, then they should be understood and evaluated in a lifecycle context for that drug.

References

Adams, C.P., Brantner, V., 2004. Estimating the costs of new drug development: is it really US$ 802m? December. Available from URL: http://media.romanvenable.net/images/drugCost.pdf (accessed June 12, 2005).

DiMasi, J.A., Hansen, R.W., Grabowski, H.G., Lasagna, L., 1991. Cost of innovation in the pharmaceutical industry. Journal of Health Economics 10 (2), 107–142.

DiMasi, J.A., Hansen, R.W., Grabowski, H.G., 2003. The price of innovation: new estimates of drug development costs. Journal of Health Economics 22 (2), 151–185.

DiMasi, J.A., Hansen, R.W., Grabowski, H.G., 2004. Assessing claims about the cost of new drug development: a critique of the Public Citizen and TB Alliance reports. November. Available from URL: http://csdd.tufts.edu/_documents/www/Doc_231_45_735.pdf (accessed June 12, 2005).

DiMasi, J.A., Hansen, R.W., Grabowski, H.G., 2005. Extraordinary claims require extraordinary evidence: reply. Journal of Health Economics 24 (5), 1034–1044.

Hansen, R.W., 1979. The pharmaceutical development process: estimates of current development costs and times and the effects of regulatory changes. In: Chien, R.I. (Ed.), Issues in Pharmaceutical Economics. Lexington Books, Lexington, MA, pp. 151–187.

Hilts, P.J., 2003. Protecting America's Health: The FDA, Business and One Hundred Years of Regulation. Alfred A. Knopf, New York, p. 213.

Light, D.W., Warburton, R., 2005a. Extraordinary claims require extraordinary evidence: comment. Journal of Health Economics 24 (5), 1030–1033.

Light, D.W., Warburton, R., 2005b. Setting the record straight in the reply by DiMasi, Hansen and Grabowski. Journal of Health Economics 24 (5), 1045–1048.

Public Citizen, 2001. Rx R&D Myths: The Case Against the Drug Industry's R&D Scare Card. Public Citizen, Washington, DC. July 23, 2001. Available from URL: http://www.citizen.org/documents/rdmyths.pdf (accessed November 5, 2004).

US Congress Office of Technology Assessment, 1993. Pharmaceutical R&D: Costs, Risks, and Rewards OTA-H-522. US Government Printing Office, Washington, DC.